GASTRO-DUODENAL ULCER

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PHYSIO PATHOLOGY, PATHOGENESIS AND TREATMENT

by

J-JACQUES SPIRA

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To the Memory of
my Father

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PREFACE

This monograph is essentially an enlarged edition of my *Causation of chronic gastro duodenal ulcer, a new theory* published by the Oxford University Press in 1931 It differs however, in the approach to the physiological aspect of the problem in as much as in the earlier communication, the behaviour of the pyloric sphincter was taken as the starting point and an original interpretation suggested which led to the postulation of the law of iso peristalsis whereas in the present contribution this sequence is reversed the behaviour of the peristaltic wave, which is examined first, leads to the postulation of the law and the deduction of the function of the alimentary sphincters as its corollary

Little advance has been made in the medical treatment since Sippy introduced his method in 1915 Failure of medical treatment has encouraged radical surgery but extensive amputation and severing of the nervous connections has not solved the difficulties and there are already indications of a return to a more conservative attitude

There appears to be no way out of the impasse

The time is, therefore, opportune for a fresh approach to the problem and an attempt to clarify the many paradoxes which confuse the student of gastro-enterology This can only be achieved by an objective examination of the available data and their systematic reassessment A sound knowledge of the fundamental principles which govern the behaviour of the gastro intestinal tract is essential for the approach to the problem and the avoidance of many errors of diagnosis

The already vast and continually increasing literature has made a drastic condensation of the subject matter imperative but a fairly comprehensive list of references which are with very few exceptions mentioned in the text has been provided In order to make it more complete the references relating to the alimentary sphincters, which are not discussed in the text, have been segregated in an Appendix

What will no doubt be considered an excessive number of references justifies itself in as much as it supports the contention that there is no observation in the literature which in any way invalidates the thesis here presented

The theoretical considerations have been fully borne out by their practical application

London

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"But there are so many facts and so many ways of arranging facts, that no one can collect facts usefully except under the stimulus of some hypothesis to which they are relevant Throughout any scientific investigations, even from the very beginning, generalising hypotheses must exist in the mind of the investigator to determine the direction of his investigations'

" and the hypotheses that prove good are very seldom such as commend themselves to our initial prejudices'

BERTRAND RUSSELL

"Science as a Product of Western Europe
The Listener, May 27, 1948

"An unrestrained adoration of figures and statistics is very often a distorted idol of our mechanical age of specialisation The figures obtained by physical and chemical means in medicine, should never replace but supplement the art of seeing, feeling and listening The idea of an 'engineer of health' is a deplorable misconception of the physician of the future It is the noble task of the academic teacher to imbue future generations of physicians with the idea that medical reasoning should never be based on arithmetical figures alone but rather should be guided by the conception that every patient is a new experience and a challenge to the keenness of our senses

SIGFRIED J THANNHAUSER

Lipidoses Oxford University Press, New York, 1950

INTRODUCTION

It is generally recognized that the incidence of chronic peptic ulcer has steadily increased during the last two decades and is fast becoming a grave social problem Apart from physical suffering, protracted invalidism, hazards to the life of the individual and prolonged unemployment add a heavy burden to the national economy

A review of the subject soon makes it evident that the primary cause of the disease has so far, eluded detection Many methods of treatment have been suggested (ranging from the extremes of starvation to high fat diets) and have no doubt achieved temporary success, but none has attained that state of permanency which could be accepted as a satisfactory solution to the problem

The student of gastro-enterology is overwhelmed by innumerable publications and perplexed by many contradictory statements Because chronic ulcer is invariably associated with an excess of acid secretion, the obliteration of the acid factor appears to be the sole preoccupation of both the medical and surgical approaches to the problem It should however, be realised that short of total gastrectomy there are no means which succeed in completely abolishing the gastric secretions thus showing clearly that all such attempts must be considered as unphysiological and should be strongly condemned

In order further to justify this affirmation it becomes imperative to clarify the role assumed by acid in the aetiology of the ulcer

The following plan has been adopted in the presentation of the subject matter which develops the argument

Part I deals with physiological considerations The motor and secretory functions of the stomach and first part of the duodenum are defined, their functional interrelations examined and deductions are drawn to provide the elements for the postulation of the Law of Isoperistalsis and its corollary the Function of the Alimentary Sphincters

Part II deals with pathological considerations It describes the evolution of the acute and chronic ulcers as aetiologically unrelated disease entities the significance of haemorrhage and perforation and the fundamental identity of gastric and duodenal ulcers which do not tend to malignant transformation The mechanism of pain is briefly considered The experimental ulcer is reviewed in order to define its contribution to the pathology

Part III deals with the pre ulcerative stage It corresponds to the intermediate or transition stage between the physiological reactions and the end result of the morbid process The normal and pathological variations of the gastric secretions are reviewed in order to establish their relation to the different forms of gastritis

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Part IV deals with pathogenesis It reviews the various factors which have been suggested as aetiologically relevant and gives the reasons for considering the Syndrome of Hyperfunction as the normal response to a morbid process It constitutes the initial contact between the physiological and the pathological and leads to the development of the author's theory of ulcer formation

Part V deals with the clinical considerations It reviews critically the orthodox medical and surgical treatments before giving the details of the author s method and its results which are illustrated by radiographs

This monograph lays down the fundamental principles for the integration of the various aspects of the problem It leads to the conclusion that chronic peptic ulcer, which is exclusive to man, is a man made disease, that it can be prevented and that, if established, it will yield to a rational diet

PART I

PHYSIOLOGICAL CONSIDERATIONS

> It is in fact an old and just criticism of physicians that they have considered the symptoms signs causes and measurements of disease without sufficient reference to the symptoms signs causes and measurements of health that they have refined their methods of detecting departures from the normal without first reviewing the idea of normal or discussing its limitations
>
> (Ryle 1947)

In this part an attempt will be made to define the limits within which fluctuations of the responses to stimuli may be considered as normal or physiological This subject will be studied very briefly in four sections the first will deal with the physical aspect or motor function, the second with the chemical aspect or secretory function the third with the correlation of these functions, and the fourth with the postulation of the Law of Isoperistalsis and its corollary the Function of the Alimentary Sphincters

CHAPTER 1

MOTOR ACTIVITIES OF THE STOMACH AND DUODENUM

(THE PHYSICAL ASPECT)

This chapter deals with the reactions which are normally concerned in the propulsion of the chyme through the gastro-intestinal tract The mechanism which regulates this function is composed of two distinct elements (1) muscular and (2) nervous

THE MOVEMENTS OF THE STOMACH

When the stomach is empty its cavity below the upper part of the fundus which is inflated with gas, is completely obliterated by the apposition of the gastric walls Food after passing through the cardia, collects just above the obliterated portion gradually separates the gastric walls, and passes downwards along the lesser curvature into the body and pyloric part of the organ (the Magenstrasse) The fundus and usually the remainder of the stomach above the middle of the body, show no peristaltic activity The muscle of this part of the organ is in a state of weak tonic contraction which is immediately inhibited by the entrance of food into the stomach—receptive relaxation—or by the presence of food in the oesophagus The pyloric part constitutes a chamber wherein the food is macerated fragmented and thoroughly mixed

THE RECEPTIVE RELAXATION OF THE STOMACH

Joseph and Meltzer (1910) observed that duodenal rhythmic activity and tonus are temporarily inhibited during each contraction of the pyloric antrum Cannon and Lieb (1911) have shown that if the gastric wall is in tonic contraction it relaxes after an act of deglutition After the relaxation which requires about 10 seconds for its full development, there is a rapid recovery of the former tonicity Repeated swallowing causes continued inhibition of gastric tonus It is an instance of reciprocal innervation of antagonistic muscles and is controlled reflexly by the vagus nerves The normal stomach possesses a marked capacity for adapting itself to the volume of its contents with only minimal change in the intragastric pressure the intrinsic and extrinsic nerves take part in the maintenance of gastric tonus (Patterson 1920) Bilateral vagotomy abolishes the receptive relaxation of the stomach (Veach, 1926)

THE MOVEMENTS OF THE INTESTINE

The classification of the motor activities of the small intestine proposed by Bayliss and Starling (1899) may be extended to include practically all types of gastro intestinal motility This classification may be summarised as follows (1) movements which are obviously reflex, including peristalsis both in the large and small intestine, and many other coordinated contractions, (2) rhythmic contractions, including gastric peristalsis, segmenting contractions in the small intestine and antiperistalsis and other rhythmic contractions in the large intestine

The propulsive movements

The propulsive movements of the intestine can be divided into three different fundamental types (1) pendular movements, (2) rhythmic segmentation and (3) peristaltic wave

The pendular movement

The pendular movements of the intestine, first described by Ludwig in 1858 (Catel, 1936), are characterised by a gentle swaying of the coils which is accompanied by rhythmical contractions They are always directed aborally (Schneller, 1925) The frequency of the pendular movement decreases from the pylorus to the ileo caecal valve (Catel 1936) The large pendular movement, which is not accompanied by any modification of calibre (Morin, 1938) and is the only unproductive movement of the colon produces a longitudinal, pendular swing of the affected bowel segment without transporting its contents (Galambos 1944)

The rhythmic segmentation

Rhythmic segmentation first described by Cannon (1898) is the most common mechanical process seen in the small intestine Cannon (1911a) described it as a sudden undefined activity which appears in a mass of food which has been lying quietly in the intestinal loops with constrictions pro ducing segments which divide while the neighbouring segments unite before the further divisions take place The constrictions do not take place in the middle of each segment but near the end

The rate of rhythmic contractions in the small intestine varies inversely with the distance from the pylorus (Alvarez 1929) from approximately 22 a minute in the duodenum to 12 a minute in the terminal ileum they are principally neurogenic in origin (Posey Brown and Bargen 1948)

The peristaltic wave

The true or coordinated peristaltic wave appears as a localised constriction of the wall of the intestine which travels downwards over a more or less extensive tract of bowel Pavlov (1910) pointed out that when the intestines are examined under normal saline the wave rarely occurs spontaneously but it can be readily elicited by inserting a suitable bolus into the lumen of the

bowel, the amount of food is the conditioning element (Cannon, 1911a) Intestinal peristalsis is annulled by the injection of nicotine into the circulation and by the local application of cocaine Since these drugs paralyse the peripheral nerve mechanisms it is inferred that the reflex is mediated through the nerve plexus of Auerbach

The peristaltic wave is distinguished from other types of waves by the fact that it produces a transport of the contents over long distances The rate of the normal peristaltic wave has been variously stated as 1 or 2 cm per minute, or even slower According to Elliott and Barclay Smith (1904) it constitutes a coordinated reaction which is characterised by a rapid propagation in the oral aboral direction Kaestle, Rieder and Rosenthal (1909) showed roentgenologically that the peristaltic waves originate near the cardia, an observation which was confirmed by Weitz and Vollers (1925) Peristaltic waves in the human stomach occur at intervals of 18–22 seconds

Schinz, Baensch and Friedl (1932) found that rapid fluid filling of the stomach produces a peristaltic wave before the stomach is full Peristalsis in the duodenum is much more rapid than normal peristalsis elsewhere in the small intestine The wave travels at the rate of 1 cm per second (Douglas and Mann, 1940) Fasting usually produces quiescence and subsequent feeding induces a rapid motor response (Douglas, 1948)

The peristaltic rush

The peristaltic rush (Meltzer and Auer 1907) or *Rollbewegungen* first described by Van Braam Houckgeest (1872) is characterised by the fact that it traverses without interruption the entire small intestine from duodenum to caecum, and is fast, in contra-distinction to the peristaltic wave which is slow and short The rate of travel of the rushes is usually from 2 to 4 cm a second, but they travel faster the farther they go, so that by the time they reach the lower ileum, they are often covering 7–25 cm a second Alvarez (1924) who could start it by making the animal swallow repeatedly or by injecting water into the oesophagus emphasised the dissociation which exists between the wave of contraction in the muscle wall and the movement of material through the lumen of the bowel

According to Cannon (1911b) the peristaltic wave is observed in two forms the first as a slowly advancing contraction which transports nutriment over a short distance and the second as a swift movement sweeping without pause for much longer distances which has the effect of emptying the canal The first form may retain the unqualified term peristalsis the second may be distinguished by the term rushing peristalsis or peristaltic rush as suggested by Meltzer and Auer (1907) According to Trendelenburg (1927) there is no difference between the peristaltic wave and the peristaltic rush

Antiperistalsis

Various contradictory observations have been made in respect of the occurrence of antiperistaltic waves Milne Edwards (1872) first described mouvements antipéristaltiques According to Van Braam Houckgeest

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bowel produced contraction above and below and that the waves travel in one direction largely because the contraction moving behind them is so lasting that there is no chance for regurgitation Hukuhara (1932) suggested that the transmission was purely myogenic

Morin (1938) believed that there are two types of movements concerned in the digestive autonomy (1) independent local elementary rhythmic contractions of both muscles (the pendular movements and rhythmic segmentation), and (2) complex coordinated expulsive reactions of the whole musculature

Krueger (1949) observed that in Thiry Vella loops in the ileum of dogs the advancing constriction of peristalsis, as described by Bayliss and Starling (1899) which is preceded by an advancing area of inhibition usually involved both a relaxation of the muscle and a complete cessation of rhythmic contractions

According to Bozler (1949) spontaneous contractions of the intestine are myogenic and are ordinarily conducted for a short distance The myenteric reflex increases this activity on the oral side and thereby propels the contents of the intestine

The peristaltic wave as a co-ordination of the two digestive muscles

Bayliss and Starling (1899) believed that when the bowel contracts the longitudinal and circular muscles respond simultaneously, the one with contraction and the other with relaxation Trendelenburg (1917) observed that stretching produced by gradually filling the small intestine produced considerable tension in the longitudinal muscle, and at the same time a contraction of the circular muscle which is transmitted orally When the critical point has been reached a peristaltic wave is initiated

The critical point is dependent on the velocity, on the increase of the tension and the tonus of the circular muscle The peristaltic wave appears to travel distally without any nervous or muscular stimulation The activity of the waves is not reciprocal but consists of two phases the first produces contraction of longitudinal muscle without manifesting either synergy or reciprocity, the second phase, initiated by the longitudinal contraction, produces contraction of the circular muscle which by a process of ' active inhibition induces the relaxation of the circular fibres According to Carey (1921) the structure surrounding the epithelial tube of the intestine in the mature state possesses a spiral nature arranged as a left hand helix with an inner close and an outer elongated set of spirals in both the submucosa and musculature Peristalsis is a duplex contraction phenomenon produced by the differential rate of translatory advance of the two contraction waves in the outer and inner muscle layer respectively Hanzlick and Butt (1928) observed a similar reciprocal response during vagus stimulation but not during sympathetic nerve stimulation Cowie and Lashmet (1929) described three primary three secondary and some tertiary types of contraction of longitudinal muscle and three types of circular muscle contraction Demoor (1931) observed that when the movements of the longitudinal and

(1872) an antiperistaltic wave can originate in any part of the gut but an antiperistaltic movement is never observed in living animals These observations have been confirmed by Cannon (1911), Trendelenburg (1917), and Ganter (1923) Borchers (1921) pointed out that antiperistalsis in the stomach is pathognomonic of pyloric obstruction, that there is no antiperistalsis during vomiting and the gastric muscles do not appear to be involved Schintz, Baensch and Friedel (1932) could not observe antiperistaltic waves roentgenologically These observations apply only to the small intestine

The law of the intestine

According to Bayliss and Starling (1899) "excitation at any point of the gut excites contraction above, inhibition below This is the law of the intestine' Cannon (1909) suggested the term "myenteric reflex' to describe this phenomenon Since this coordinated action could not conceivably be performed by muscles alone, Bayliss and Starling inferred that it was controlled by Auerbach's plexus, possibly by short augmentor paths extending upwards and long inhibitory paths reaching downwards Usually these waves moved in a downward direction an effect which they suggested might result from higher excitability at the duodenal end True peristalsis they regarded as a coordinated reflex, consisting of combined contraction and relaxation, dependent on the proper functioning of the local nervous system Bayliss and Starling (1901) found that when the intestine was painted with cocaine and nicotine the true peristaltic movements ceased, but the pendular movements continued

Magnus (1904a), who separated the longitudinal from the circular muscle, observed that the former (to which Auerbach's plexus adhered) retained the power of rhythmic movement while the latter had lost it He concluded, therefore, that the pendular movements are not reflex but neurogenic in origin When he seared the outer surface of the circular muscle with crystals of silver nitrate (Magnus 1904c) physostigmine produced rhythmic contractions which he concluded were myogenic Gunn and Underhill (1914) pointed out that the conditions of Magnus's experiments were not the same as those of Bayliss and Starling and concluded from their own experiments that spontaneous rhythmicity is an inherent property of the muscle observations which were confirmed by Alvarez and Mahoney (1922a) According to Thomas and Kuntz (1926) these experiments only indicate that the intestinal muscle is capable of rhythmic contractions in the absence of nervous influences but they do not prove the muscular origin of rhythmic movements of the stomach and intestine in the intact animal

Wheelon and Thomas (1922) considered that the progressive nature of the cycles of events which showed a fixed time relationship between the antrum, the sphincter and the first part of the duodenum, which they observed graphically, demonstrates 'the law of the intestine' i e, a progressive band of constriction preceded by inhibition and followed by relaxation Alvarez (1929) believed that the downward peristalsis can take place without the help of the myenteric reflex because stimuli applied to the outer coat of the

centre of the stomach similar to the nodes of the heart, and he believed that it initiated the rhythmic contraction of the stomach He suggested that food is propelled through a series of zones or segments, each furnished with its own pace maker and its own rhythmical contractions Alvarez (1915) supported this conception because he noted that on electrical stimulation of different portions of the stomach wall the lesser curvature near the cardia displayed the shortest latent period as compared with the other structures of the stomach and that the test for irritability yielded similar results

Cole (1917, 1932) observed radiologically in man that the period of opening of the pylorus and the passage of the fluid content into the duodenum was coincident with the tonus rhythm of the stomach fluid chyme being expelled through a relaxed pylorus as each contraction reached it. He described cycles of rhythmic systole and diastole When peristaltic activity is weak, pyloric closure is at a minimum, when strong the pylorus is tonically closed Luckhardt Phillips and Carlson (1919) observed that during digestion the peristaltic waves course towards the pyloric sphincter and on reaching it, relaxation occurs The passage of the contraction wave from the stomach over the pyloric sphincter to the duodenum, i e. the existence of a relation between gastric and duodenal motility has been described by Wheelon and Thomas (1922) McCrea McSwiney Morison and Stopford (1924) observed in the open abdomen or roentgenologically waves which began near the cardia travelling aborally According to Cunha (1925) the gastric wave passes from the stomach over the duodenum. Ivy and Vloedman (1925) observed that the distal portion of the duodenal cap contracts following the arrival of a vigorous gastric wave at the pylorus

Klein (1926a) believed that there was sufficient evidence to assume that there is a gastric pace maker At the re-entrant angle (the commencement of the antrum) there is a separate nodal centre which initiates the antral contractions

Thomas and Crider (1935) found in dogs with cannulated gastric and duodenal fistulae a progressive decrease in the gastric influence as the distance from the pylorus increased They confirmed the observation of Ivy and Vloedman (1923) that the duodenum participates in the hunger activity which is interrupted with the first presentation of food and is associated with the receptive relaxation of the stomach

According to Painter, Todd and Kuenzel (1939) pyloric rhythm seems quite independent of gastric peristalsis but is closely coordinated with the rhythm of the duodenal cap *An open pylorus and cap diastole go together* and a closed pylorus and cap systole

The polarity of the bowel

The polarisation of the intestinal tract appears to be so strong that although liquid can be pumped into the rectum of cats or dogs until it flows out of the mouth any attempt to force a solid body like a tampon or a stick in an oral direction through a segment of the living bowel is likely to result in tearing on account of the resistance developed (Bayliss and Starling

circular muscles are recorded separately the aqueous extract of the one muscle tends to produce the characteristic features of the other in their autonomous or induced activity, and that chemical factors cannot, therefore, be completely excluded from the normal regulation of the movement of the gut Krishnan (1932–33a) deduced from his graphic records that the nature of peristalsis depends on a reciprocal innervation in the two muscular coats Goerttler (1932), who could not find any signs of Carey's muscle spirals, suggested that the muscular fasciculi in the circular layer form true rings while those in the longitudinal coat run parallel to the mesenteric attachment However, Reid, Ivy and Quigley (1934) and Franklin and Maher-Loughman (1938) confirmed the observations of Carey

According to Raiford and Mulinos (1934–35) stimulation of the mucosa of the colon causes a contraction of the longitudinal muscle at and below the point of stimulation but none above, and contraction of the circular muscle at and above the point of stimulation but none below Vagus stimulation by mucosal irritation elicits contractions of the longitudinal muscle first, and then the circular, 3–5 seconds later The result of such a mechanism is first to increase the lumen of the gut and then to decrease or obliterate it Morin (1935), who confirmed the observations of Trendelenburg (1917), observed that distension of the lumen rather than the tension on the longitudinal muscle initiates the peristaltic wave

The peristaltic cycle

Hofmeister and Schütz (1885) divided the gastric cycle into two parts during the first part, the peristaltic wave begins on the greater curvature, a few centimetres from the cardia, and then passes downward growing gradually deeper until it reaches the sphincter antri, the second phase begins with the contraction of the sphincter antripylori, while the pre antral contraction is reflected the antral sphincter contracts and cuts off the antrum from the stomach and at the same time the longitudinal and circular muscles contract These observations on the dog were confirmed by Holzknecht (1909) in the human

Barbera (1898) found that the first contraction always appeared at the cardia, regardless of whether the stimulus was applied to the cardia, to the fundus or to the antrum, and that this contraction was then followed by a typical peristaltic wave According to Auer (1908) the first phase of a contraction appears in the stomach near the oesophageal insertion and travels peristaltically to the sphincter antri During the second phase the sphincter antri contracts strongly, and during this contraction the rest of the antrum contracts *in toto*, moving towards the pre antrum and expelling the antral contents largely, or entirely into the pre antrum Kirschner and Mangold (1911) saw a complete synchronisation in the antral contractions and the opening of the pyloric sphincter, causing the latter to bulge markedly

Keith (1915) observed a distinct modification of the musculature and the plexus just distally to the junction of the oesophagus and the stomach a definite development of neuro-muscular tissue which might serve for a nodal

centre of the stomach similar to the nodes of the heart, and he believed that it initiated the rhythmic contraction of the stomach He suggested that food is propelled through a series of zones or segments, each furnished with its own pace maker and its own rhythmical contractions Alvarez (1915) supported this conception because he noted that on electrical stimulation of different portions of the stomach wall the lesser curvature near the cardia displayed the shortest latent period as compared with the other structures of the stomach and that the test for irritability yielded similar results

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The polarity of the bowel

The polarisation of the intestinal tract appears to be so strong that although liquid can be pumped into the rectum of cats or dogs until it flows out of the mouth any attempt to force a solid body like a tampon or a stick in an oral direction through a segment of the living bowel is likely to result in tearing on account of the resistance developed (Bayliss and Starling

1899) It is generally accepted that the original direction is maintained in all segments which have been reversed If certain worms are cut across in small pieces, these pieces crawl in the same direction towards the point where their head used to be (Carlson, 1904) Biederman (1904, 1905 1906) stated that in the earthworm, the leech and the snail there is no evidence of a direct muscle conduction of the peristaltic wave but that it depends on the integrity of the central nervous system and follows mostly segmentally advancing reflexes in which a passive stretching of a segment produces, by a reflex action, a contraction of the circular muscle and an inhibition of the longitudinal muscle If a segment of ciliated epithelium of the frog's mouth is reversed and regrafted the cilia will continue to wave in the original direction (Brücke 1916) Segale (1921) found that gas cannot easily be forced through reversed segments That liquids can only be forced through with difficulty is shown by the fact that, in the reversal experiment, the muscle in the segment immediately forward to the upper suture lines always hypertrophies markedly Gellhorn and Weidling (1926), using frogs found that in the stomach and intestine conduction of a stimulus was faster in a caudal than in an oral direction Nolf (1929) found that in a nicotinised segment of small bowel in chicks, a wave would travel when it was stimulated at its oral end but gave only a local reaction when stimulated at the aboral end of the segment Ide (1934) reported on the study of Lauwers and Damnyanovitch who found that the reversal of the whole small intestine produces death in from 4 to 5 days while the reversal of the ileum only established a certain tolerance With complete destruction of the afferent and efferent (extrinsic) nerves with a concentrated solution of ammonia the animal survived 10–18 weeks

Alvarez (1929) observed a gradient in the activity, tonus, irritability, metabolism, electrical potential and rate of rhythmic contraction along the small bowel from the duodenum to the end of the ileum, the gradient of forces in the bowel making it easier for waves or impulses to travel in an oral–aboral direction He believed that gradients are not an adjustment to function but intimately built into the structure of the bowel Few workers have, however, been able to verify Alvarez hypothesis (Morin, 1938)

The effect of food on motility emphasizes the polarity of the bowel Best and Cohnheim (1910a, c) observed that when water was introduced, through a gastrostomy, into the stomach of a dog with an oesophageal fistula in the neck, sham drinking would produce a more rapid emptying of the water in the stomach than would normally take place, and that sham feeding will also prevent the backflow into the stomach when fat is introduced into the duodenum through a fistula In the experiments of Cash (quoted by Pavlov, 1910) a bolus moved through the intact intestine of a laparotomized animal during fasting at the rate of 0 1–0 5 cm per minute, but after feeding the speed was 1 5–2 cm per minute Hurst (1912) has shown that a barium meal will move down the bowel faster when it is followed by a second meal given shortly afterwards Hines, Lueth and Ivy (1929) found that there is increased muscular activity of the small bowel after eating when the colon is full Rabe (1925) has shown in dogs that inflammatory conditions in the

caecum or colon will fail to slow the emptying of the stomach if the source of irritation is kept below the ileo-caecal sphincter which forms the natural boundary between the small and large intestine When food was ingested the movements of an exteriorised intact loop of the intestine were increased (Barcroft and Robinson 1929) Hoelzel (1930) observed the rates of passage to be more or less proportional to the specific gravity of the test materials heavier materials passing slower than light materials

Puestow (1931, 1932) observed in an exteriorised segment of the duodenum containing the papilla of Vater, that it was relatively inactive in the fasting state and became definitely more active after feeding There was also an increase of hyperaemia and an apparent increase of duodenal secretion The responses were greatest in the duodenal segments less marked in the jejunal portions of the bowel and least noticeable in the lower part of the ileum The onset appeared earliest in the duodenum and the latent period increased proportionately to the distance down the intestinal tract at which the segment was isolated

Quigley, Highstone and Ivy (1934) found that the intestinal propulsive activity when conditions were unchanged, was practically constant (1 5 cm per minute) the propulsion rate in loops of the lower ileum being slightly slower than in the upper jejunum Cannon (1936) suggested that there may not be a gastro-colic reflex, only an appetite or a taste reflex since food given by mouth passes on quicker than when given through a gastrostomy Gianturco (1933a) could not see any difference between the rate of emptying when his cats ate and when they were fed by tube

Douglas and Mann (1939) found in exteriorised loops of the lower part of the ileum of the dog that in normal animals the loop was as a rule, quiescent after a 48 hours fast While the short-circuited loop usually showed a correlation of activity and feeding the completely isolated loop never did so Their findings indicated that the mediation of the motor effect depends on the continuity of the intestine and that it varies directly with the distance from the pylorus They concluded that the so-called gastro ileac reflex is not merely a feeding reflex, that it depends for its mediation on the continuity of the intestine and that the vagus nerves play little part in the mediation Observations by Douglas and Mann (1940) on exteriorised loops of jejunum, ileum and colon suggested that following the ingestion of food a wave of activity travelling at the rate of 1 cm per second passes down the length of the small intestine and is not abolished by vagotomy The motor activity appears first in the segment nearest the stomach (Grindlay and Mann 1941)

Van Liere Stickney and Northup (1945) observed the rate of progress of a charcoal mixture through the small intestine of frogs, at the end of 8 minutes it had traversed 54 cm of the length of the small intestine at the end of 15 minutes 121 2 cm and at the end of 30 minutes 154 6 cm thus indicating that the upper half of the small intestine has a more active propulsive peristalsis than the lower

Douglas (1949) measured the rate of rhythmic contraction of exteriorised segments in continuity of jejunum in dogs Transplantation of end to-end

anastomosis of the exteriorised segment of the lower ileum was followed by a persistent fall in the rate of contraction A similar fall occurred after isolation of a segment or after proximal transection and re anastomosis or after proximal hemisection Clamping the gut or infiltration with procaine was followed by a fall in rate distal to the site of interference but by no change proximal to it The results suggested that rhythmic activity of the duodenum and jejunum were coordinated

The inherent polarity of the smooth muscle fibre was observed in embryo chicks by de Jong and De Haan (1943)

The polarity of the nervous impulses

Hooker (1917) studied the polarity of the nervous elements in frog embryos by the removal of a portion of the spinal cord and by regrafting it in the reverse direction, he observed that the reversed segment continued to grow in the original direction

Nolf (1929) excised an intestinal loop about 12 cm in length and suspended it in oxygenated Ringer s solution in such a way that one of its extremities emerged slightly above the surface of the bath When the oral extremity was stimulated a peristaltic wave started at the electrode and progressed through its whole length even when the loop was formed by the small intestine from the pylorus to the ileo caecal junction If on the other hand, the aboral extremity was stimulated the contraction never extended over more than 10 cm from the stimulated point The speed of the propagation in the oral-aboral direction did not go beyond 25–30 cm per second at a temperature of 37° C These observations are explained on the assumption of the existence in the intestinal wall of a longitudinal nervous pathway from one extremity to the other, which is interrupted by synaptic relays These are placed in such a way that the stimuli pass without difficulty in the oral–aboral direction, but not in the reverse direction This deduction was further verified by the action of nicotine which has the effect of blocking the synapses without affecting the neuromuscular junction

THE MOVEMENTS OF THE INTESTINAL MUCOSA

The movements of the isolated muscularis mucosae consist of regular, slow rhythmic contractions occurring at the rate of 1 in 27–60 seconds (Gunn and Underhill 1914) The villi possess two distinct movements that are independent of peristalsis (1) a lashing movement which is not stopped by atropine and (2) an alternating retraction and extension which is abolished by both nicotine and atropine (Hambleton, 1914)

According to King and Arnold (1922) the intestinal villi manifest rhythmical movements shortening lengthening and lateral or swaying movements both singly and in groups the movements of the individual villi occurring independently or together with movement of the mucosa as a whole The intestinal mucosal motor mechanism is set into activity by mechanical stimulation by heat, irritants and by adrenaline pilocarpine atropine nicotine and barium it is very sensitive to anaemia and comparatively

short lived Impulses by way of the vagi usually do not reach the mucosal musculature The splanchnics carry tonus impulses to the mucosa, Meissner s plexus is looked upon as a terminal splanchnic mechanism and a local reflex tonus mechanism There is no definite interdependence of correlation between the activities of the outer and mucosal motor mechanism The mucosal motor mechanism is most active and reactive in the duodenum and upper jejunum and less so in the lower jejunum and almost refractory in the ileum Impulses from the mucosa, when the musculature is in tonus bring about relaxation The reaction of the intestinal mucosa to stimulation is local in character and myogenic in origin (an observation confirmed by Wells and Johnson, 1934) Kokas and Ludany (1934) observed that the sympathetic first stimulates before it inhibits the villi to keep them in a state of contraction, while the vagus inhibits their movements to keep them in a state of relaxation

THE MECHANISM OF INTESTINAL AUTONOMY

The elements which are concerned with the mechanism of gastro-intestinal autonomy are (1) the muscular layer and (2) the nervous system

The Muscular Layer

Muscle layers of the stomach

The musculature of the stomach is formed by three layers—the longitudinal the circular and the oblique muscle fibres

Forsell (1912) has described two axes of support (Stützsysteme) of the stomach situated outside the stomach to which the musculature is attached as if it were arranged round a skeleton The transverse axis is formed by the ligamenta pylori and is supported by the pylorus which he considered to be extra gastric The vertical axis consists of two parts both attached to the oesophageal wall (extra gastric) one formed by the oblique muscle band the other by the medial longitudinal band (Cravatte de Suisse) he prefered to label them ligamenta ventriculi rather than ligamenta pylori He described the bands of the pyloric antrum as the lower segment sling and accepted the existence of the horse shoe sling of Seber

Brown and McSwiney (1926) described three layers which may be distinguished in the muscular coat external middle and internal The external layer consisting of longitudinal fibres which are continuous with the corresponding fibres of the oesophagus and duodenum is best developed over the greater and lesser curvature between these regions the fibres are thin and scattered The middle layer is made up of circularly arranged muscle fibres which are continuous with those of the corresponding layer of the oesophagus and duodenum They radiate outwards and upwards in the fundus from the thickened band of circular fibres forming the cardiac sphincter at the junction of the oesophagus and stomach The internal layer is represented by a muscular band on each side of the lesser curvature passing from the fibres of the cardiac sphincter to the circular coats of the pyloric antrum

Muscle layers of the intestine

The muscular element in the intestine is composed of the longitudinal and the circular muscle fibres, which constitute the wall of the gut

Structure of the plain muscle

The muscle layers of both the stomach and the intestine are formed by plain muscle The muscles are made up of splindle shaped cells which vary in size, shape and number of nuclei in different animals and different parts of the same animal In the case of smooth muscle there is a double nerve supply, one variety being motor and causing contraction (parasympathetic), the other kind inhibitory and causing cessation of a previous contraction (sympathetic)

Reactions of smooth muscle to environment

The changes of environment which have a direct influence on the function of the muscles of digestion are determined by mechanical and by physiochemical reactions

The smooth muscle fibre has the property of exhibiting different lengths while exhibiting one and the same degree of tension (Sherrington, 1915) Smooth intestine muscle reacts only when the muscle fibres are stretched It has elastic and mechanical properties similar to skeletal muscle Bozler (1940) believed that relaxation is not produced by an inhibitory mediator, but is a purely physical process controlled alone by the visco elastic properties of the contractile elements

A characteristic of smooth muscle is its ability to maintain a firm and lasting contraction without fatigue The maintenance of the sustained tonus is apparently not associated with increased expenditure of energy (Evans, 1923) The tissue is very sensitive to alterations in the hydrogen ion concentration The effect of increase of hydrogen ion concentration within limits compatible with life, is to cause relaxation of tone, in muscle preparations devoid of tone it has no effect (Evans and Underhill, 1923)

Plain muscle is extremely susceptible to changes in *temperature* As a rule warming causes relaxation while the application of cold causes a tonic contraction

Smooth muscle is very sensitive to *mechanical stimulation* and may respond by a local or a general (propagated) contraction One form of mechanical stimulation is that produced by tension The effect may be twofold, first extension then excitation with increased contraction A stimulus applied to any part of a sheet of plain fibres may travel all over the sheet that is produce a wave of contraction, just as if it were a single fibre Each fibre of smooth muscle gives an all-or none response to a stimulus feeble stimuli produce only local contractions According to Fletcher (1937) the action potential is followed by a contraction of the muscle which varies directly with the size of the action potential Rosenblueth and Rioch (1933) found that a partial destruction of the nerve supply impairs the responses of smooth muscle less than those of skeletal muscle to indirect electrical stimulation, the contractions

of smooth muscle being a function of the number of nerve impulses delivered per unit of time and not of the number of nerve fibres involved Slight stretching of plain muscle produces rhythmic contractions, in the small intestine they are regular frequent and powerful and are myogenic (Ferguson 1940)

The chemistry of contraction in plain muscle is very similar to that of striated muscle Glycogen disappears and lactic acid arises when the muscle contracts (Evans 1926) Sodium bicarbonate stimulates and carbon dioxide depresses pendular rhythm and peristaltic rhythm (Sollmann v Oettingen and Ishikawa, 1928) Changes of pH within the range of 8 2–6 8 have little effect on intestinal movements an increase causing a rise and a decrease causing a lowering in tonus (Suckow and Burget 1929) High dilutions of hydrochloric acid inhibit the spontaneous contractions which are restored by sodium bicarbonate (Gorman Dreier and Rehfuss 1931)

The Nervous System

According to Bichat (1830) two great systems exist in every vertebrate the one concerned with the outside world represented by organs of locomotion and external sense organs to which he gave the name *animalic*, the other concerned with the regulation of the nutrition of the body which he called *organic* Each of these systems had its own central nervous system the cerebrospinal regulating the animalic and the sympathetic ganglia regulating the organic system The nerve fibres of the sympathetic are non medullated (Remak 1838), the rami communicantes are partly grey (sympathetic) and partly white (cerebrospinal) thus producing a reciprocal connection between the two nervous systems (Müller 1840)

The nervous element which is concerned in the function of the gastrointestinal tract is part of the autonomic system which was divided into tectal bulbosacral and sympathetic systems by Langley (1898) He considered that each had a different development history and later suggested (Langley, 1921) a classification of which the sympathetic the parasympathetic and the enteric systems formed the three divisions The sympathetic was represented by the thoraco-lumbar and the enteric by the plexuses of Auerbach and Meissner, while the parasympathetic was represented by the ocular (tectal) and bulbosacral or oro-anal (bulbar and sacral) division

According to Cannon (1930) the external environment of the body is controlled by the voluntary or exterofective system and the internal environment by the involuntary or interofective system which establishes homeostasis

The autonomic nervous system

The autonomic nervous system consists of the ganglia that are anatomically and functionally connected with the central nervous system through the visceral efferent components of the cerebral and spinal nerves and the nerves that arise in these ganglia Afferent cerebrospinal nerve components

are functionally associated with the autonomic nerves, but these are not regarded as part of the autonomic nervous system, since they are essential components of the cerebrospinal nerves The peripheral visceral efferent conduction pathway consists of two neurones, a visceral efferent cerebrospinal nerve component and an autonomic neurone, the former may be designated the preganglionic neurone, the latter the ganglionic neurone On the basis of the distribution of the preganglionic neurones in the central nervous system, the autonomic nervous system may be divided into (1) the cranial division, which is connected with the brain stem through preganglionic components of the third, seventh, ninth, tenth and eleventh cranial nerves, (2) the thoraco-lumbar division, which is connected with the spinal cord through preganglionic components of the thoracic and first and second lumbar spinal nerves, and (3) the sacral division, which is connected with the spinal cord through preganglionic components of the second, third and fourth sacral nerves

The preganglionic components of the thoracic and upper lumbar nerves join the sympathetic trunk through the white communicating rami and terminate either in the ganglia of the sympathetic trunk or in sympathetic ganglia located in closer proximity to the abdominal viscera (the prevertebral ganglia), those of the cranial and sacral nerves do not join the sympathetic trunk but run directly to the peripheral ganglia in which they terminate The cranial and sacral divisions of the autonomic system are comparable to each other but differ from the thoracolumbar division in respect of their preganglionic connections and their reactions to certain drugs (adrenaline and atropine) On the basis of these anatomical and physiological peculiarities, the cranial and sacral divisions have been designated the cranio-sacral autonomic system, and the thoraco-lumbar division the thoraco-lumbar autonomic system The former constitutes the parasympathetic, the latter the sympathetic system The parasympathetic system comprises the cranial autonomic ganglia and all the autonomic ganglia associated with the thoracic, abdominal and pelvic viscera which are connected with the central nervous system through preganglionic components of the vagus and sacral nerves, and all the nerve fibres arising in these ganglia The sympathetic system comprises the sympathetic trunk ganglia and the ganglia in the coeliac and other abdominal and pelvic plexuses that are connected with the central nervous system through preganglionic components of the splanchnic nerves, and all the nerve fibres arising in these ganglia The preganglionic neurones that connect the ganglia in the walls of the enteric canal with the central nervous system are components of the vagus and sacral nerves These ganglia are, therefore, related to the parasympathetic system Many of their neurones however are not related to preganglionic neurones by direct synaptic connections but are components of local reflex arcs (Kuntz, 1946)

Nervous control of the gastro-intestinal canal

The nerves taking part in the gastro-intestinal function are the intrinsic and extrinsic nervous systems Gaskell (1916) considered that there is no difference between extrinsic and intrinsic nerve cells both are motor or

inhibitor cells of the involuntary nervous system which have travelled out from the central nervous system to reach their destination

Anatomical distribution of the autonomic nervous system

The intrinsic (or intra mural) system

This is composed of (1) the sub-serous plexus which does not contain any neurones—the removal of which appears to have no disturbing influence on the autonomy According to Hill (1927) it is largely sensory in function (2) the sub-mucous plexus (Meissner)situated between the mucosa and the circular muscle, more developed in the intestine than in the stom ach, and (3) the myenteric plexus (Auerbach) which is situated between the two muscles more developed in the stomach than in the intestine

The plexuses of Meissner and Auerbach have been classified by Langley in a separate division which he called the enteric *nervous system* They are ontogenetically anatomically and physiologically related to the parasympa thetic division of the autonomic nervous system but possess the capacity for independent functional activity in a greater degree than other parts of this system. The cells of Auerbach s plexus are arranged in groups along the intestine nerve fibres coming from the vagus according to Gaskell (1916) but from the sympathetic according to Dogiel (1895) make connection with many of these ganglia by means of collaterals The plexuses of Auerbach and Meissner are connected by bundles of fibres which run up at irregular intervals through the circular muscle layer (Hill 1927)

It has been suggested that the local ganglionic cells of the stomach are composed of unmyelinated fibres which may be partially sensory (vagus) and partially pre-ganglionic (sympathetic) According to Waddell (1928–29) reflex arcs exist within the wall of the intestine

In the stomach both the myenteric and the submucous plexuses exhibit the same general plan of structure as in the small intestine According to Irwin (1931) both the fibre bundles and the ganglia are small and few in the cardiac region but increase materially both in size and number towards the pylorus The submucous plexus is more abundantly developed in the stomach than in the oesophagus but includes relatively few ganglia According to Patzelt (1936) both autonomic divisions participate in the formation of synapses but the majority of entering fibres are parasympathetic Pre ganglionic vagus fibres terminate in synaptic relationship with enteric neurones The pre ganglionic fibres in the splanchnic nerves terminate in the coeliac and other pre vertebral plexuses The post ganglionic fibres which originate in the coeliac plexus and enter the walls of the stomach and intes-tine do not make synaptic contact with enteric neurones but terminate on the gastro-intestinal musculature (Thomas and Kuntz 1926b)

Sinha (1949), using a buffered 1 20 000 solution of silver nitrate at pH 8 4 claims that it stains the enteric plexuses specifically and demonstrates the existence of multipolar nerve cells with long processes that branch and rebranch but with relatively few nerve fibres in the submucous plexus After

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produces an increase in the amplitude, frequency and tonus of the muscular contraction of the gut but relaxation of the sphincters

The two vagus nerves which connect the bulb with the stomach provide the motor supply which is not due to the transmission of impulses through the myenteric plexus one vagus nerve being sufficient to give the entire stomach a motor supply (Ducceschi, 1905)

According to Courtade and Guyon (1899) *the vagus first stimulates the* longitudinal fibres of the stomach the primary effect, then stimulates the circular fibres the secondary effect, at the cardia and pylorus stimulation of the longitudinal fibres produces relaxation of the circular fibres

Nicotine permanently abolishes the action of vagus impulses on the intestine (Bayliss and Starling 1899) Moderate stimulation of the vagi at first produces a lessening of the tonus of the muscle and a diminution in the amplitude of the contraction The inhibitory action is short and is followed by an augmentor effect after which both tonus and waves return to their initial state Repeated stimulation of the vagi produces a more permanent increase in tone When both nerves are sectioned the first effect is total supression of peristalsis Langley s (1898–99) observation that the body of the stomach and pylorus received inhibitory as well as motor fibres from the vagus was confirmed by May (1904) According to Cannon (1911) the function of the vagi is that of setting the muscles in a tonic state If the vagi are cut the phenomenon of receptive relaxation does not occur

McCrea, McSwiney and Stopford (1925) and McCrea (1926) have shown that the vagus may have either a motor or an inhibitory influence on the stomach the type of reaction being dependent on the pre-existing condition of the peripheral mechanism McCrea, McSwiney and Stopford (1926) suggest that the nerves of the parasympathetic system to the stomach consist of one type of efferent fibres and are not divided into motor and inhibitor nerves If the response of the gastric musculature to vagal impulses is determined by the condition of the wall, then inhibition of the functional activity of the stomach cannot be due to division of the vagi, and symptoms of such inhibition if present, can only be accounted for by the unopposed action of the inhibitory sympathetic fibres

McSwiney and Wadge (1928) showed that the vagal effect of the stomach *depended on the tonus of the musculature* Veach Schwartz and Weinstein (1930) found that for moderate degrees of tonus low frequencies produced motor effects whereas high frequencies were inhibitory a high degree of tonus favoured the production of inhibition with both low and high frequencies These reactions were to be expected in view of the similarity of vagal inhibition to Wedensky inhibition Stimulation of the vagus in the neck (Tournade 1936) produces two phases hyperkinesia followed by hypokinesia

Alvarez (1937) has suggested that as the presumed synapse can be blocked by small doses of nicotine or by anoxaemia the fibres of the vagi do not end in or near the muscle fibres but act through the mediation of Auerbach s plexus

sympathectomy, there appeared slight changes in the cell bodies of the myenteric plexus, the outline of the cell bodies appeared blurred and their nuclei were situated extrinsically These changes were not seen after vagotomy

The extrinsic (or extra mural) nervous system

The stomach and intestines receive their extrinsic innervation from three regions of the central nervous system (1) the bulb, (2) the sacral cord, and (3) the thoraco lumbar origin of the sympathetic Both the bulbar and the sacral systems of nerves are, in general, motor The bulbar system, through the vagi, innervates the canal from the oesophagus to the end of the ileum, diminishing in influence as it descends, the sacral system, starting at the anal end reaches upwards along the colon, with diminishing influence as it ascends Opposed to these two motor systems is the sympathetic, distributed to the same areas, and acting in the main to inhibit what they stimulate (Langley, 1903)

According to Irving, McSwiney and Suffolk (1937) the gastric and duodenal mesenteries are innervated by the vagus and splanchnic nerves while the jejunal mesentery appears to be supplied by the splanchnic nerves

If the classification of the neural regulation of the intestine into intrinsic and extrinsic factors is accepted as a matter of convenience rather than as a matter of fact, one can consider, according to Hammett (1921), that the intestinal mechanism primarily stimulated in the normal unexcited animal (albino rat) is the motor mechanism mediated by the vagus as the extrinsic nerve, while in the excited animal the stimulation is effective through the inhibitory mechanism mediated by the more truly extrinsic nerves, the splanchnics, thus differentiating these activities from the so called intrinsic mechanism involved in the myenteric reflex

The extrinsic nervous system is composed of three parts (1) the efferent pathways, (2) the afferent pathways, and (3) the centres The *efferent* pathways consist of the vagi and the splanchnics which represent a double system, the former, motor augmentary, are bulbar or sacral in origin, the latter, motor inhibitory, are dorso lumbar in origin The *afferent* impulses are trans mitted through the vagi which are the nerves of sensibility (Carlson, 1915) and the vagi and splanchnics (Irving, McSwiney and Suffolk, 1937) The *centres* connecting the efferent and afferent pathways are situated in the spinal cord but have not been accurately localised

It is generally, although not unanimously, accepted that vagotomy retards and splanchnicotomy accelerates intestinal transit Total denervation produces, on balance, retardation pointing to the predominant effect of the vagi over the sympathetic (Morin, 1938)

The function of the extrinsic nerves

The function of the vagus nerves

The effect of vagus stimulation, as reported in the vast literature, has been variable, most observers reported increase of motor function and tonus It has been generally taught that stimulation of the left and right vagus nerves

produces an increase in the amplitude, frequency and tonus of the muscular contraction of the gut but relaxation of the sphincters

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The function of the sympathetic nerves

The more primitive the animal the less conspicuous becomes the sympathetic system In the lowest group of vertebrates the sympathetic cells are so few that they cannot be described as forming a system, their place is taken by the masses of chromaffin cells, which form a scattered but segmentally arranged system in the very position occupied in the higher animals by the sympathetic system There is in the literature considerable disagreement as to the effects of stimulation of the sympathetic system upon the movements of the stomach Both inhibitor and augmentor effects have been described

According to McCrea (1926) it would appear that the splanchnics regulate the "postular tonus" of the stomach, having an augmentor action on the inactive and an inhibitor action on the active stomach

The effects on the longitudinal and circular muscles are, according to Hukuhara (1936), both motor but with different latent periods Stimulation of the splanchnic nerves results in inhibition of peristalsis of the wall of the gut and diminution of tone, while the sphincters contract

It is generally accepted that stimulation of the sympathetic supply to the gastro intestinal tract is predominantly inhibitory but excitatory effects are often obtained, particularly in the stomach (McSwiney,1931), and that it also produces vasoconstriction in this region Stimulation of the sympathetic nerves according to Brown and McSwiney (1932) produces a chemical mediator which may have either a stimulating or an inhibitory effect on the stomach According to Patterson and Rubright (1934) the effect of splanchnic stimulation on the cardiac sphincter is always contraction in the dog inhibition in the rabbit, while in the monkey contraction or inhibition may occur according to the state of the initial gastric tonus

Bozler (1940) who pointed out that since the same excitatory and inhibitory effects are produced by adrenaline, the results cannot be explained on the assumption of specific excitatory and inhibitory nerve fibres, he suggested that excitation and inhibition represent two phases of the action of the same nerve impulses, and that it also produces vaso constriction in this region There is evidence that no serious digestive upset follows complete removal of the sympathetic ganglia and chains in cats dogs and monkeys, and it has long been known that bilateral splanchnic section does not appreciably affect gastric activities and therefore the sympathetic supply does not contribute any essential factor to normal gastric motility or tone (Cowgill, 1941) Bingham, Ingelfinger and Smithwick (1950a) observed kymographically that after pre ganglionic sympathectomy for hypertension the motility was clearly decreased in the early post operative period later, a slight increase was apparent

Afferent impulses from the stomach are carried by the splanchnic nerves (Cerqua 1935, Bain Irving and McSwiney, 1935)

Relation of the vagus and sympathetic nerves—the autonomic balance

According to Hammett (1922) the nerve endings of the vagal mechanism are affected by a predominant hydroxyl ion concentration while the splanch-

nic endings are affected by a predominant hydrogen ion concentration

Koennecke and Meyer (1922) found that the action of the vagus is preponderant in the stomach and the sympathetic in the small intestine They rejected the conception of antagonistic action of the vagus as the motor and the sympathetic as the inhibitor nerve According to Thomas and Wheelon (1922) stimulation of the vagus leads to motor responses in about 90 per cent of the trials and to inhibitory responses in 10 per cent In the case of the splanchnic nerves, stimulation leads to motor responses in 63 per cent of the trials and to inhibitory responses in 37 per cent

Carlson, Boyd and Pearcy (1922) and Carlson and Litt (1924) considered that the view of a simple antagonistic action of the vagus and the sympathetic systems is not tenable for the cardia the stomach and the pylorus

According to Zondek (1929) physiological antagonistic action between the vagus and the sympathetics is possible only when the electrolyte ratios (calcium to potassium, magnesium to sodium) are maintained

McCrea and MacDonald (1928) have shown on cats and dogs that the effects produced by the intravenous administration of *sympathomimetic* (adrenaline ephedrine, ergotamine) and *parasympathomimetic* (pilocarpine physostigmine, acetylcholine) drugs, like stimulation of the splanchnic or vagus vary with the tone of the viscus but do not closely duplicate the effects of faradic stimulation According to Alvarez, Hosoi Overgaard and Ascanio (1929) both the vagi and the splanchnic serve as inhibitors and regulators of intestinal activity

From embryological studies on *Rana pipiens* Van Campenhout (1929) concluded that the neural crest represents the exclusive source of sympathetic elements, the visceral branch of the vagus nerve is derived from the medullar neural crest and the nervous elements in the intestinal wall are related to the sympathetic system The small intestine from the pylorus on is innervated primarily by sympathetic branches and there is no evidence of any participation of the vagus nerves as late as the eighth day of incubation when the intestinal walls show a perfectly developed nervous supply with myenteric and submucous plexuses While many authors consider the vagi as the primary origin of the intrinsic nervous system of the digestive tract Van Campenhout (1930) attributes the essential role to the thoraco lumbar sympathetic system and the origin of the intra visceral nervous ganglia from a differentiation of mesoblastic cells or from a migration of elements from the thoraco-lumbar ganglionic crest (Van Campenhout 1931)

Kiss (1931) demonstrated that the local ganglionic cells of the stomach are composed of unmyelinated fibres which may be partially sensory (vagus) and partially pre ganglionic (sympathetic)

He found six to eight small nerves joining the superior cervical ganglion and the plexiform ganglion (gangl nodosum vagi) the majority of fibres being unmyelinated, and he compared these anastomotic fibres with the white and grey rami communicantes of the spinal nerves He believed that the effective (motor and secretory) nerve of the abdominal organs is exclusively sympathetic that the coeliac and all other prevertebral ganglia belong exclu

sively to the sympathetic, that the so called parasympathetic influence of the vagus has no anatomical basis in the case of the abdomen, and that the parasympathetic phenomenon can only be a parasympathetic phase of the sympathetic

According to McSwiney (1931) the sympathetic and parasympathetic nerves regulate two different types of response of the stomach (1) pure tonus changes, as evidenced by contraction or relaxation of the muscle fibres, (2) augmentation or inhibition of rhythmic movements

It would appear, however, that the immediate effects of vagotomy, splanchnicotomy and denervation of the stomach are similar, namely, retardation of function After a period the peripheral intrinsic nervous mechanism assumes control and only one permanent symptom—decrease in initial emptying time—is observed From the histological evidence of the enteric plexuses and nerve endings it would appear that the vagus nerves end in aborisations around cells of Auerbach s plexus while the postganglionic fibres of the sympathetic end in association with the muscle fibres McSwiney and Robson (1931) found that, under certain conditions, reversal of the sympathetic response was recorded

McSwiney and Spurrell (1932–33) tested Kiss's conception of the arrangements of the autonomic fibres in the vagus in cats They obtained typical gastric responses to vagal stimulation in those deprived of the superior cervical ganglion or stellate ganglion and found that stimulation of individual bundles of the vagal roots produced results which only varied quantitatively from those of the whole nerve No evidence was obtained for the existence of special groups of motor or inhibitor fibres

Lalich Meek and Herrin (1936) observed that the reflex gastric inhibition could be mediated by either the vagi or splanchnics Each set of nerves contained both afferent and efferent nerves but their evidence indicates that inhibition is more easily induced over vagal pathways

Tinel (1937) stated that the opposition of the sympathetic and parasympathetic nervous systems is neither rigorously constant nor absolute and that these systems do not constitute true physiological entities, on the contrary, each one represents a complex group of functions and systems which are not always synergistic Their activities may vary considerably and under certain conditions may be greatly modified and even be completely inverted It should be remembered, however, that the sympathetic of the anatomists is not always the same as the sympathetic of the physiologists and that in the same system can be encountered fibres with different functions and even physiologically opposed characteristics There is plurality of functions in addition to plurality of systems

According to Morin (1938) the extrinsic nervous system coordinates the autonomous activities of the peripheral end organs through a reflex autoregulation Total denervation produces on balance, retardation, pointing to the predominant effect of the vagi over the sympathetic It is generally, although not unanimously accepted that vagotomy retards and splanchnicotomy accelerates intestinal transit

Babkin (1944) considered that the actual classification of the autonomic nervous system should be based much more on the functional relationship between a nerve and an organ than on purely morphological data and it is preferable in many instances to speak of adrenergic or cholinergic nerves rather than to classify them rigidly as sympathetic or parasympathetic

According to Kuntz (1946) the visceral organs, with certain exceptions, which are innervated through both the sympathetic and parasympathetic divisions of the autonomic nervous systems, are synergistic in function The concept of a clear-cut functional difference between the parasympathetic and the sympathetic nerves is untenable Feldberg (1954) considers the parasympathetic as the efferent pathway for visceral reflexes when the viscera are localized the sympathetic as the efferent pathway where the viscera are widespread He believes that the antagonism of the action of the two systems has been over-emphasized in the past

According to Mitchell (1953) the vagus nerves from the neck downward intercommunicate frequently with sympathetic ganglia and nerves and they are in fact mixed sympathetic parasympathetic nerves The vagus and sympathetic trunk are fused in the upper cervical region in the dog and are enclosed in a common epineural sheath (Mizeres 1955) Communicating fibres between the vagus and the sympathetic in the cervical region in the human have been described by Imperato and Hinton (1955)

According to Imperato, Reid and Hinton (1956) there are preganglionic cholinergic fibres in the greater splanchnic nerves whose relationship to the gastric secretory apparatus is similar to that of cholinergic fibres in the vagus

It may perhaps be suggested that since the parasympathetic and the sympathetic nervous systems contain both motor and inhibitory fibres, when one of these systems is artificially excluded the other system, in addition to its own function, gradually assumes the function of its antagonist in an attempt to re-establish a functional equilibrium

The hypothalamus

The hypothalamus (diencephalon) is probably concerned with the integrated control of both the sympathetic and parasympathetic system and the secretion of the posterior lobe (neural division) of the pituitary

According to Cushing (1932) there is a strong suggestion of the presence in the diencephalon of a parasympathetic centre apparently tuberal in situation According to Kabat and his colleagues (1935) there is a centre in the hypothalamus more particularly in the lateral hypothalamic area which inhibits gastro-intestinal motility

Wang Clark Dey and Ranson (1940) observed (in fasting cats) vagal effects on the gut when the hypothalamus at or behind the infundibular level was stimulated and these were not abolished after bilateral vagotomy According to Sheehan (1940) adequate stimulation of the hypothalamus particularly in the more posterior part of the lateral hypothalamic area always produced an immediate inhibition of peristalsis and complete loss of tone, there was never any indication of increase in motility

Cortical regulation of autonomic function

The cerebral cortex and the corpus striatum influence autonomic discharge, the highest level of the motor outflow is that of the hypothalamus which gives rise to the supra-optico-hypophyseal system The cortical regions involved in the regulation of autonomic functions include mainly the motor and premotor areas There is extensive overlapping of the areas involved in autonomic and somatic motor functions, making possible a high degree of correlation between visceral and somatic reactions The autonomic responses to localized cortical stimulation are less definitely circumscribed than the somatic responses since stimulation at a single point may result in a widespread discharge through the autonomic nerves There are no circumscribed cortical areas for sympathetic and parasympathetic reactions respectively but the character of the autonomic response to stimulation of any appropriate cortical area seems to be determined by the physiological state of the animal and the physiological state of the cortex at the time of stimulation (Crouch and Thompson, 1939)

The mechanism through which impulses emanating from the cerebral cortex influence visceral functions is not fully known The fibres of cortical origin through which these impulses are conducted probably terminate mainly in the diencephalon and at lower levels in the brain stem Much of the cortical influence is exerted through the phylthalamus and the available data, particularly those which indicate exaggerated autonomic activity following cortical ablation, support the assumption that the influence of the cerebral cortex on visceral functions is predominantly inhibitory Direct stimulation of the cortex in intact animals sometimes elicits autonomic activation, but more commonly autonomic inhibition The exaggerated autonomic activity commonly observed following cortical lesions indicates the release of the autonomic centres in question from the inhibitory influence of the cortex

THEORIES OF THE AUTONOMY OF THE GASTRO-INTESTINAL TRACT

Following the review of the muscular and nervous elements which are concerned with the gastro intestinal motor function, the theories which have been suggested to explain their autonomy may now be summarised

Myogenic theory

Bayliss and Starling (1899) believed that peristaltic movements were neurogenic but that the segmenting ones were myogenic Cannon (1911) considered that the observations by Bayliss and Starling that the rhythmic contractions are myogenic are not conclusive because it is conceivable that the short augmentor paths and the long inhibitory paths which they assume are, in fact, superintending fibres in the wall of the canal He quotes Magnus

(1903) whose first argumentation against Bayliss and Starling s contention was based on the distinction between the local motor centres for muscular action and the conducting paths uniting these centres The fact that atropine paralyses conducting paths, but not the centres, whereas cocaine paralyses the motor centres before stopping conduction, suggested that the drugs used by Bayliss and Starling, although destructive to the machinery of the local reflex, did not seriously injure the immediate nerve supply and that the rhythmic contraction might result from rhythmic nervous discharge

The second argument of Magnus was supported by the observation that when the longitudinal and circular muscle layers are pulled apart Auerbach s plexus adheres to the longitudinal layer Under these circumstances the longitudinal muscle alone manifests spontaneous rhythmic contractions The circular muscle deprived of the plexus although capable of responding to a single mechanical stimulus by a single contraction, never shortens rhythmically (Magnus 1905) Sick and Tedesco (1908) separated from the stomach pieces of longitudinal muscles without the nerve plexus which then no longer contracted spontaneously The behaviour of the intestinal muscles with or without their nervous plexus shows important differences, the independent muscle can be tetanized, it gives superimposed contractions, has no refractory period and manifests no rhythmic response to continued stimulation On the other hand, muscle preparations with the plexus attached cannot be tetanized are clearly refractory to weak stimulation during the period of shortening and the first part of the period of relaxation and with continued stimulation exhibit rhythmic contraction

The myogenic theory of Alvarez and Mahoney (1922) stated that the smooth muscle fibre possesses the inherent property of autonomy The arguments in support of their theory are based on the experiments of Magnus (1904, 1905) who after completely isolating the circular muscle from all its nervous connections, showed that these fibres regain their rhythmical activity Morin (1938) observed that it is difficult to say with complete certainty that all nervous elements can be destroyed to provide the means for testing the theory It would certainly explain the local reactions which are non propulsive and non coordinated

Neurogenic theory

The arguments in favour of the participation of the parietal nervous system are the experiments of Bayliss and Starling (1899) Cannon (1909) Trendelenburg (1917) and Morin (1935) which are concerned with the coordination of the peristaltic movement in the denervated gut, the distal transmission and the polarization of the peristaltic waves (Bayliss and Starling 1899 Cannon 1912 Henderson 1928), the results of the pharmacological exclusion of the plexus the action of cocaine and nicotine on the denervated and isolated intestine are incompatible with independent peristalsis (Bayliss and Starling 1899 Trendelenburg 1917, Krishnan, 1932–33), the embryological evidence provided by the observation that in the guinea pig embryo intestinal movements appear only on the 28th day of intra uterine life

simultaneously with the appearance of the intrinsic nervous system, the observation that there appears to be no constant relation between the mechanical and electrical activity in the isolated strip of intestine (Berkson, 1933, Puestow, 1933)

Myo-neurogenic theory

The opposition of the myogenic and neurogenic theories is more apparent than real, different mechanisms being responsible for different functions while their combination is responsible for their complete function The local reaction of the longitudinal fibre (pendular movements) and circular fibre (rhythmic segmentation) is dependent on the properties of the muscular cell while the coordinated and polarized peristaltic wave requires a nervous regulation

Humoral elements which intervene in the regulation of the activity of the gastro-intestinal tract concern the production of (1) acetyl choline, and (2) adrenaline

Cohnheim (1890), working on isolated intestine, concluded that the extrinsic nerves are not the initiators of gastro intestinal movements, the intestinal tract itself possesses the means to produce stimuli which keep up its function which is autonomous or facultatively autonomous and the mechanisms which produce the common gastric and intestinal movements are situated in the muscle wall of the stomach and intestine The nervous and humoral correlations are concerned only with the regulation of this function According to Alvarez and his colleagues (1929) both vagi and the splanchnics serve as inhibitors and regulators of intestinal activity The gastro intestinal tube possesses a large degree of autonomy and the neuromuscular mechanisms responsible for orderly 'diastalsis' must be looked for in the bowel itself

Cannon and Rosenblueth (1937) stated that because of their double innervation the organs under tonic control of the autonomic system can be made to alter the degree of their functional use either as an integrated group, through sympatho adrenal influence or as separate structures through the direct effects of parasympathetic impulses

The sympathetic division of the autonomic system, despite its extensive range of action is not essential for existence The two ganglionic chains, as well as the prevertebral ganglia have been removed from animals and yet within the confines of the laboratory such altered animals seem not to differ markedly from the normal (Cannon McIver and Bliss, 1924) When they are exposed to heat or cold however, or when subjected to lowering of blood sugar, or tested by loss of blood through haemorrhage, they show definite deficiencies (Sawyer and Schlossberg 1933)

The cranial division of the autonomic system may be regarded as protective, conservative and upbuilding in its services to the organism and is responsible for the augmented tone of gastric and intestinal musculature which is established when that state is favourable for the peristaltic and segmenting motions which are essential for the digestive process

According to Morin (1938), in addition to the autonomy which is inherent in the smooth muscle of the intestine there is an intrinsic and extrinsic nervous mechanism which regulates its function Although a strip of intestine may continue to react rhythmically when it is stretched, the longitudinal and circular fibres are not capable of a coordinated activity and expulsive effect unless they are regulated and directed by the myenteric plexus which represents the intrinsic (intramural) nervous regulation This mechanism is sufficient to allow the intestine to assume *in vitro* all the movements it is capable of *in vivo* for the protection of the living organisms For the establishment of an autonomous and harmonious equilibrium, it is necessary to bring into play the extrinsic (extra mural) nervous system One can visualise that according to its intensity, the mechanical stimulus induces either a local myogenic reaction or a progression limited by the intrinsic nervous system, or regulatory reactions which re-establish the normal condition of tension

CHAPTER 2

SECRETORY ACTIVITIES OF THE STOMACH AND DUODENUM

(THE CHEMICAL ASPECT)

GASTRIC AND DUODENAL SECRETIONS

Secretory cells of the gastric mucosa

The secretions of the gastric mucosa are produced by a variety of cells which are composed of four major types (Hollander, 1936–37)

(1) The mucous cells of the surface epithelium secrete a viscous mucus which, on coagulation, gives rise to strings and clots of mucin

(2) The peptic cells (also called *body, chief,* or *central*) which secrete the enzymes or their precursors

(3) The parietal cells (also known as *Belegzellen, acid, oxyntic,* and *delo morphous cells*) which contribute the hydrochloric acid

(4) The neck chief cells, which secrete a mucoid substance (Babkin, 1931)

Secretory glands

The glands of the stomach may be classified according to their distribution

(1) The cardiac glands which occupy a small area near the cardiac orifice of the stomach

(2) The main gastric glands which occupy the fundus and the body part of the pyloric region The ducts are short and the alveoli are long the latter are lined by two types of cells (a) by the peptic cells which secrete pepsinogen and (b) the parietal cells which secrete hydrochloric acid

(3) The pyloric glands which begin at the incisura angularis on the lesser curvature and a point considerably nearer the pylorus on the greater curvature The ducts are long and the alveoli are short They secrete an alkaline mucus which is poor in chloride They resemble in many respects Brunner s glands of the duodenum with which they are in direct continuity

The acidity of the gastric contents is due entirely to the secretion from the *main gastric cells the parietal cells being exclusively concerned in its produc* tion Using various staining reactions it has been shown that the secretion in the parietal cells is slightly alkaline but that the lumen of the gland is practically neutral The acid is therefore formed entirely above the level of the gland proper namely, in the foveolae and on the surface

Topographical distribution of the secretory glands of the stomach

Brenckman and Deloyers (1929b) studied the topography of the secretory surface of the stomach by means of the Prussian blue reaction They found that the corpus is the region which elaborates the hydrochloric acid, the demarcation of the antral region is clear-cut and corresponds to the cytological differentiation of the two sectors The air pouch of the fundus does not participate in the secretion of the acid even after surgical reduction of the gastric pouch Deprived of its circulation the stomach does not produce hydrochloric acid, in a fasting state it does not give the Prussian blue reaction while, following a gastro-enterostomy of the corpus there is a reduction of the secretory process in the immediate neighbourhood of the os

The parietal cells in normal and pathological human stomachs are distributed fairly uniformly over the corpus of the stomach In the cardia and fundus their number is decreased by about 50 per cent, at the incisura angularis (angle) their total is 75 per cent of that of the corpus There is no significant difference in the average number of parietal cells on the posterior and anterior surfaces of the mucous membrane of the corpus The transition from corpus glands to pyloric glands is usually abrupt on the lesser curvature just above the angle of the stomach while on the greater curvature it is more gradual (Berger, 1934)

The *Magenstrasse* first described by Waldeyer (1908), corresponding to the longitudinal groove which descends along the lesser curvature from the cardiac zone to the pyloric part of the stomach, has been given prominence in gastric pathology because it is one of the most frequent sites of gastric ulcer It is said that the mucous membrane of the *Magenstrasse* is thinner than that of other parts of the corpus but it appears probable that this peculiarity of the stomach is due to mechanical causes, particularly to fixation and has no specific significance from the secretory point of view

The pyloric part secretes continuously at an average of only 2 0–2 5 cc per hour of moderately alkaline fluid (*p*H 7–7 50) whereas the glands of the fundus and corpus may discharge 50–60 cc or more per hour of strongly acid gastric juice (Babkin 1944) The secretion is mucoid, viscous tenacious transparent odourless and slightly salty to taste In appearance and consistency it is best compared with egg white Neither food nor drink influence the amount of the secretion, whether or not the nerve supply of the pyloric pouch is intact (Ivy and Oyama 1921)

Meulengracht (1935) has shown that the pyloric portion of the gastric glandular system is concerned with the production of the anti anaemic factor and not with the digestive juices

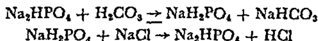
Morrison (1938) suggested that the oxyntic cells may secrete the anti anaemic principle as well as hydrochloric acid

According to Sheldon and Grossman (1948) one type of cell in the body of the frog s gastric glands secretes both acid and pepsin

Formation of hydrochloric acid

Several theories have been advanced to explain the chemical processes

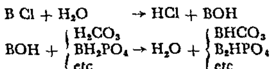
concerned in the formation of hydrochloric acid from the blood chloride The following simple equations appear to give a satisfactory explanation of the reactions which are involved in the process



$$Na_2HPO_4 + H_2CO_3 \rightarrow NaH_2PO_4 + NaHCO_3$$
$$NaH_2PO_4 + NaCl \rightarrow Na_2HPO_4 + HCl$$

There are two opposite views regarding the method of production of hydrochloric acid by the parietal cells of the gastric mucosa According to one view the parietal cells do not secrete hydrochloric acid as such but produce a precursor which is converted into hydrochloric acid in the tubules of the gland or on the surface of the gastric mucosa (Bensley, 1932) The other view is that hydrochloric acid is formed within the parietal cells either in that portion of the cytoplasm which is immediately adjacent to the canalicular wall or more probably in the wall itself (Hollander, 1943) According to Bull and Gray (1945) hydrochloric acid arises from an exchange of organic anions for chloride ions A somewhat similar view was held by Conway, Fitzgerald and Walls (1945) Rehm (1945) has shown by experiments on the live dog, that the rate of acid secretion of gastric mucosa can be increased by passing through it an electrical current which enhances the natural potential difference, and decreased by a current of opposite direction These results were confirmed on the frog by Crane and Davies (1947), Crane Davies and Longmuir (1946 1948a, b), and Davies and Ogston (1950) Rehm and Hokin (1947) observed a decrease of potential difference across the stomach wall which was associated with the onset of the secretion of hydrochloric acid Bradford and Davies (1948) demonstrated that the intracellular canaliculi which form a network just below the surface of the oxyntic cells contained acid during acid secretion showing that the acid is formed in the region between the canaliculi and the external cell wall (pericanalicular zone) Davies and Longmuir (1948) have suggested that stimulation of active acid secretion without sufficient CO_2 to neutralise the alkali formed in the oxyntic cells may be operative in the causation of some types of acute human gastric ulcers

Hollander (1949) postulated the existence in the parietal cell, of a membrane which is permeable only to water hydrogen ion and chloride or related ions, and he suggested the following chemical reaction at the wall of the canaliculus (B representing the usual cations)



$$BCl + H_2O \rightarrow HCl + BOH$$
$$BOH + \begin{cases} H_2CO_3 \\ BH_2PO_4 \\ \text{etc} \end{cases} \rightarrow H_2O + \begin{cases} BHCO_3 \\ B_2HPO_4 \\ \text{etc} \end{cases}$$

Rehm (1950) proposed the following theory of the formation of hydrochloric acid

(1) The electromotive forces of the mucosa send electric current across the canalicular border of the parietal cells in the direction of the canaliculi

(2) This flow of current in the presence of a gastric stimulant results in the production of H^+ ions

(3) The flow of current can control the production of H^+ ions, without furnishing a major portion of the free energy needed for the osmotic work involved in the formation of the H^+ ions

(4) The return flow of current would be in the opposite direction and the flow of current in this direction results in the transport of Cl^- ions from the interstitial fluid to the gastric juice

Davies (1951) after reviewing the early hypotheses (1) processes based on electro-chemistry (2) processes based on inorganic chemistry and (3) processes based on organic chemistry, and the recent theories (1) the function of carbonic anhydrase in oxyntic cells and (2) the organic acid theories, and also the source of the hydrogen ions, the electric activity of the gastric mucosa, the metabolism of the acid secreting gastric mucosa, concludes that two related mechanisms of acid secretion are possible In the first mechanism the metabolic hydrogen atoms from glucose and water which are transported by the dehydrogenases become oxidized to hydrogen ions at the cytochrome level, and the electrons react with oxygen and water to form first hydroxyl ions and then bicarbonate ions by further reactions with carbon dioxide This process uses the redox energy from the level of atmospheric oxygen to that of the cytochromes In the second mechanism phosphate bond energy generated by reactions at lower redox levels is utilized to concentrate hydrogen ions formed by ionization from water, in an electron cycle mechanism in which hydrogen ions are reduced to covalent hydrogen atoms transported by a carrier system and oxidized to hydrogen ions at high concentration as a result of a coupled phosphorylation Kinetic and thermodynamic considerations show that the hydrogen carrier and electron transport systems could be oxalo-acetate malate and cytochrome b or perhaps fumarate succinate and cytochrome c Both mechanisms require a spatial array of enzymes in the pericanalicular zone of the oxyntic cells and in both cases chloride ions move in the opposite direction to, and as a result of, the movement of the electrons carried by the cytochromes The rate of transport of water by the oxyntic cells is so enormous that it could not be handled molecule by molecule by any known enzyme systems The water must be moved in bulk, and probably flows osmotically as a result of the secretion of the hydrogen and chloride ions by the oxyntic cells

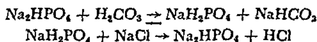
For a fuller discussion of the subject *see* Collip (1922) Dawson and Ivy (1925, 1926), Apperly and Crabtree (1931), Robertson (1931) Browne and Vineberg (1932), Davenport (1943 1946), Davies (1948) Rehm and Hokin (1949) Patterson and Stretton (1949), Friedman (1951) Davies (1952), Conway (1953)

The constituents of the gastric secretion

The gastric juice is a mixture containing several specific constituents

Hydrochloric acid — This is essential for peptic digestion peptic activity

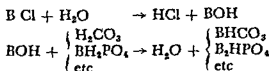
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cells is a very slightly hypertonic solution of virtually pure hydrochloric acid, having a titrimetric acidity around 0 17 N and a pH around 0 87 It contains extremely little, if any, ash or organic solids of any kind, and its composition is practically independent of its rate of formation, the intensity of the stimulus and probably even of the character of the stimulating agent The combined acidity, neutral chloride, inorganic phosphate, and various organic substances invariably encountered in mixed gastric juice all derive from non acid buffer containing secretions pepsin, mucus, the hypothetical mucoid or dilution secretion and even small amounts of transudate which enter the interstitial spaces These constitute the "non acid component of the gastric juice

Uropepsin — This is a proteolytic enzyme resembling gastric pepsinogen which occurs in the urine of normal animals and man A high protein diet markedly increases its urinary output (Bucher, 1947) Functioning gastric mucosa is necessary for its presence in the human, it is reduced or absent in pernicious anaemia (Farnsworth, Speer and Alt, 1946)

Gottlieb (1924) found that uropepsin tended to be highest in subjects who had hypernormal gastric acidities and was reduced or absent with achlor hydria The level in the urine depended on renal function and was diminished in nephritis when the blood level was raised

After surgical destruction of the gastric mucosa in the dog (Matthes 1903) or total gastrectomy in the dog (Bucher 1947), in the cat (Bucher and Ivy, 1947), in the rat (Balfour, Preston and Bollman, 1948) and in the human (Poldore, Broh Kahn and Mirsky, 1948), uropepsin disappears rapidly from the urine Bucher and Anderson (1948) believed that the amount of uropep sin is unrelated to the quantity of gastric juice secreted Peptic ulcer patients may fall into two groups with either normal or high outputs (Block, Rosen berg, Broh Kahn and Mirsky, 1948) Gastric pepsin is closely mirrored by uropepsin and ketosteroid excretion Low levels are found in pernicious anaemia carcinoma of the stomach, cirrhosis of the liver, high levels in peptic ulcer (S J Gray, reported in Lancet, 1 337, 1956)

Pure gastric juice is a clear limpid colourless fluid It has a specific gravity of slightly over 1 It is laevorotatory The freezing point is about –0 56° C, which is similar to that of pancreatic juice, hepatic bile and succus entericus, and is practically the same as that of the blood The determination of the freezing point of different digestive juices affords some indication that various glands exhibit different degrees of permeability to constituents of the blood

The constituents of the upper duodenal secretion

Babkin (1928) reported that in Pavlov s laboratory it was found that the duodenal juice contained pepsin and rennin like enzymes Florey and Harding (1934) found a pepsin like enzyme in the juice from a duodenal fistula in the goat and in the dog According to these authors the distribution, cellular constitution and staining properties of Brunner s glands vary from species to species The mucus secreted in the duodenum is a product of Brunner s glands (Florey and Harding 1935)

rapidly falls when the amount of free acid present sinks below 0 08 per cent, but an increase in the free hydrochloric acid above the average normal does not lead to any increase in peptic activity

Pepsin — In the presence of hydrochloric acid pepsin breaks down proteins to peptones Pepsin is secreted by the chief or peptic cells, early investigators believed that it occurred in the form of pepsinogen which, under the influence of the hydrochloric acid, was converted into pepsin Pepsin has been obtained in crystalline form from bovine gastric juice (Northrup, 1932–33) and pepsinogen from swine mucosa (Northrup,1937) Pepsin is present at birth, extract of the cow s stomach has digestive power in an acid solution from the third foetal month

Mucin — This is a typical mucoprotein (Webster and Komarov, 1932) which, according to Babkin (1944) is responsible for the stability of pepsin, preserving it from destruction by the hydrochloric acid, and it may protect the gastric mucosa from autodigestion According to Webster and Komarov (1932) mucoprotein differs from mucus of the surface epithelium, being a *sui generis* chemical body The average mucin content is 0 5 per cent and is slightly higher after a test meal than in the fasting stomach (Brummer, 1946)

According to Glass and Boyd (1949) mucin is a mixture of dissolved mucoprotein—a product of mucoid chief cells of the gastric glands of the body and fundus and dis olved mucoproteose—mainly derived from the digestion of the gastric surface epithelium mucus

Histamine — Brown and Smith (1935) found a histamine like substance in human gastric juice

Acetylcholine — Bloch and Necheles (1938) found that gastric juice con tained (1) acetylcholine, (2) a substance which lowers the blood pressure even after administration of atropine and contracts the isolated strip of intestine, and (3) a substance with apparently toxic properties relaxing the intestinal strip

Rennin — Dotti and Kleiner (1938 1942–43) stated that it is generally accepted that pepsin and rennin are distinct and different enzymes, but by using the phenomenon of the digestibility of rennin by pepsin as a basis for the detection of rennin they found that no rennin was present in the gastric juice of human adults

When empty the reaction of the human stomach is faintly acid or may even be neutral

There is no evidence of the presence of gastric lipase or fat splitting enzyme

Austin and Gammon (1931) stated that the gastric juice is not quite uniform throughout the stomach By separately analysing secretions secured from different portions of the organ, they demonstrated that juice from the fundus contained a high concentration of free hydrochloric acid, with little sodium and nitrogen the secretion from the pyloric end was neutral and contained almost equal amounts of sodium and chloride but far more nitrogen than fundic juice

According to Hollander (1949) the fluid normally secreted by the parietal

inhibition of gastric secretion Carlson (1913) found that the inhibition is initiated by stimulation of nerve endings in the gastric mucosa and not by mechanical tension or pressure on the stomach wall

Gastric secretion is inhibited by pituitary and adrenal hormones (Rogers, Rahe, Fawcett and Hackett, 1915–16), by thyroid feeding (Hardt, 1916, Truesdell 1926, Chung, Chang and Sloan, 1927) Hess and Faltitchek (1925) observed increased free and total acidities and gastric motility after para vertebral injection of novocain suprarenin which did not occur after splanchnectomy in peptic ulcer cases They observed a decrease after the injection of ergotamine but Coelho and Oliveira (1928) and Pieri and Tanferna (1932) observed an increase in secretion

Volborth and Kudryavzeff (1927) demonstrated that the splanchnic nerves contained secretory fibres for the gastric glands, while the depressive influence of the sympathetic nerves on gastric acidity was indicated by Moll and Flint (1928–29)

Baxter (1934) found that stimulation of freshly cut splanchnic nerves produces a secretion of mucus with a low peptic power Adrenaline first inhibited but later increased the spontaneous secretion of mucus Stimulation of the gastric mucosa of the frog by mechanical means by adrenaline, but not by pilocarpine or acetylcholine, elicited secretion of both acid and pepsin through reflex activity mediated by the splanchnic nerves (Friedman, 1937)

Babkin (1944) stated that stimulation of the splanchnic nerves and adminis tration of adrenaline (by injection, by mouth in the intestine, or gastric pouch) provoke gastric secretion although much less than stimulation of the vagi Oberhelman, Woodward, Smith and Dragstedt (1951) found that when gastric secretion is measured quantitatively in vagus innervated, total pouch dogs, sympathectomy produces a definite and significant increase in the 24 hour output of hydrochloric acid and an increase in the quantitative secre tory response to insulin hypoglycaemia and to a standard dose of histamine These increases were not observed at all, or were very meagre in amount in animals with absent or relatively deficient vagus innervations of the stomach These findings suggest that the sympathetic nerves to the stomach contain inhibitory fibres which presumably act on the vagus secretory mechanism

Nervous coordination

The secretory activity (of mixed glands) is not regulated *en masse* but various nerves or chemical agents stimulate or inhibit each set of secretory elements separately (Thomas 1943) According to Kuntz (1946) the chief and parietal gland cells in the fundus are innervated by both parasympathetic and sympathetic fibres which excite and sympathetic fibres which inhibit secretory activity The parasympathetic fibres exert the major influence in the secretion of water and hydrochloric acid in this part of the stomach while the sympathetic secretory fibres play but a secondary role in this function The sympathetic secretory fibres exert the major influence in the secretion of enzymes while the parasympathetic fibres play but a secondary role in this function

According to Wright, Jennings, Florey and Lium (1940) an abundant secretion of alkaline mucoid juice is produced in the upper part of the duodenum (in acute cat preparations) by (1) stimulating the vagi, (2) cutting the splanchnic nerves in the thorax, and (3) administering eserine either alone or with acetylcholine A scantier secretion is produced by the intravenous injection of material containing secretin The consistency of the juice obtained by any of these methods is indistinguishable from that of juice from permanent duodenal fistulae, though the cellular content varies with different methods of stimulation The secretory activity of the first part of the duodenum is under both nervous and hormonal control

THE REGULATION OF GASTRIC SECRETION

The regulation of the gastric secretion is effected by the coordination of three different mechanisms (1) the nervous control, (2) the chemical control, and (3) the hormonal control

Nervous control of the gastric secretion

Secretory fibres for the stomach are formed in the vagi and splanchnic nerves It is generally held that each individual type of gland cell is innervated by a distinct group of nerve fibres which act selectively through normal or pathological reflexes and influence separately the secretion of mucus, pepsin or hydrochloric acid

Function of the vagi

Secretory impulses from the mouth cavity to the gastric glands are transmitted reflexly through the vagus nerves When food is introduced directly through a stomach tube or a gastric fistula into either an innervated or denervated stomach, it produces a gastric secretion of smaller volume and of lower acidity and peptic power than when it is ingested normally through the mouth (Babkin, 1928) Rhythmic stimulation of the vagi by a strong induction current in the dog (Vineberg, 1933) produces a gastric secretion which is (*a*) copious in volume, (*b*) of high free and total acidity, (*c*) of high total chloride content, (*d*) fairly rich in mucus, and (*e*) of exceptionally high peptic power The peptic power of the "vagus gastric juice is much higher than that of gastric juice secreted under any other conditions (Babkin 1944) Lim and Moser (1951) observed that if the pylorus is vagotomized, the sham feeding response is reduced and pyloric cocainization no longer brings about its total inhibition Thus vagal stimuli to the fundus can excite gastric secretion independently of gastrin

Function of the splanchnics

The effects of stimulation of the splanchnic nerves on gastric secretion in animals and man are very contradictory

The sympathetic nervous system appears to be mainly concerned with the

gastric secretion in the cat and in man They further observed (1) that the gastric response to histamine or alcohol is greatly enhanced and prolonged after caffeine administration, and (2) that the gastric secretory response to histamine or alcohol and caffeine administered simultaneously is considerably greater than the sum of the preceding individual responses to the same doses of histamine or alcohol and caffeine given separately The response to the combined action of these drugs is prolonged and maintained at a high level

FOOD CONSTITUENTS

The gastric mucosa can be stimulated to form gastric juice by the local chemical action of various food substances The gastric digestion of foods such as meat casein and egg white liberates secretagogues which excite gastric secretion by local contact with the gastric mucosa (Pavlov, 1910, Savitch and Zeliony, 1913 Ivy and Javois 1924b, Lim, Ivy and McCarthy, 1925, Farrell, 1928a, Cowgill and Smith, 1932–33)

ALCOHOL

Gastric secretion may be provoked by oral (Cheney, 1928) intra intestinal (Ivy and McIlvain, 1923 Cheney 1928) rectal (Frouin and Molinier, 1901 Radzikowski 1901) and intravenous (Petrovitch and Bokanova, 1929, Newman and Mehrtens, 1932) administration of alcohol Dilute solutions (less than 15 per cent) stimulate a gastric secretion of high acidity and low peptic power (Babkin, 1928) Dragstedt, Gray Lawton and Arellano (1940) suggested that alcohol produces its stimulating effect on the gastric secretion by the liberation of histamine Wangensteen Varco, Hay, Walpole and Trach (1940) noted that alcohol when instilled into a jejunostomy, enterostomy, caecostomy or colostomy exerted a stimulating effect on the gastric secretion of man High concentrations of alcohol irritate the gastric mucosa and provoke the secretion of mucus The prolonged administration of high concentrations may produce atrophic gastritis (by dehydration or destruction of the glands)

WATER

It has been suggested by several authors that water is a gastric stimulant Drinking water on the part of the thirsty animal nearly always causes secretion of gastric juice Pavlov (1910) has shown that 400–500 cc of water introduced into the stomach produces a small secretion of gastric juice in the Pavlov pouch If only 100–150 cc is injected no secretion appears in the Pavlov pouch Neutral solutions pass into the intestine very freely depending on the evacuation time small quantities of water leave the stomach soon after ingestion with a practically neutral reaction (Stewart and Boldyreff, 1932) Sutherland (1921a) suggested that the response of the gastric glands to water introduced intravenously is mainly a general tissue reaction controlling hydraemia The composition of the juice as compared with histamine juice shows greater concentration of total chloride and acid with pepsin and mucus much increased Bergeim Rehfuss and Hawk (1914) have claimed

Chemical control

The gastric secretions are a direct function of the quality and quantity of the food ingested The mechanism which is concerned with the secretory function is dependent on the direct or indirect reactions produced by agents which have a stimulating or inhibitory effect on the gastric glands

Chemical stimulation (secretagogues)

The chemical stimulants of gastric secretion can be divided into two classes (1) those which act by direct contact with the gastric mucous membrane (a local effect), and (2) those which act indirectly through the blood stream (a systemic effect) Reference will be made only to the most important stimulants

HISTAMINE

Histamine is the most important chemical stimulant of the gastric secretions It acts directly on the secretory glands of the stomach without participation of the secretory nerves, it acts when administered by mouth (Ivy, McIlvain and Javois, 1923, Lim, Ivy and McCarthy, 1925) but not when introduced into the duodenum (Popielski, 1920) or the intestine (Rothlin and Gundlach, 1921) In man, as much as 100–225 mg of histamine by mouth may be required to stimulate gastric secretion (Ivy and Javois, 1925c)

Nicotinic acid is said to have a histamine like effect on gastric secretion

The effect of histamine on pepsin secretion shows conflicting results (Berndt and Ravdin, 1934) No increase of output in dogs was observed by Babkin and Vineberg (1931), Gilman and Cowgill (1931), Bowie and Vineberg (1935), Alley (1935), and Necheles (1949), but an increase was found by Rivers and Vanzant (1937) and Bucher and Ivy (1941)

After repeated administration the gastric mucosa is temporarily refractory to histamine stimulation

Friedman, Pincus, Thomas and Rehfuss (1943–44) observed that the introduction of acid into the small intestine provoked the secretion of pepsin from the stomach but that this effect was absent following the administration of histamine

Injected subcutaneously it stimulates gastric secretion It is generally used in a dose of 0 5–1 0 milligram as a test for the secretion of hydrochloric acid

PILOCARPINE

Pilocarpine stimulates the secretion of pepsin but is not quite a true parasympathetic stimulant Given subcutaneously it produces a volume rate response comparable to a low dose of histamine and yields a pepsin output five times that of histamine, when pilocarpine and histamine are given together a summation of the effects of the two drugs is observed in the volume output (Bucher, Ivy and Gray, 1941) Administration of pilocarpine is also accompanied by the secretion of gastric mucus in considerable quantity (Hollander and Stein, 1943–44)

CAFFEINE

Roth and Ivy (1944) have shown that caffeine is a potent stimulant of

gastric motility, large doses to diminish it This controversial subject has been reviewed by Kirsner and Palmer (1940) and Ivy (1941)

Adrenaline and *ephedrine* depress gastric motility and secretion (Rafferty, Van Liere and Sleeth, 1937) A denervated Thiry fistula is much more sensitive to adrenaline than an innervated one in the same dog (Youmans, 1938)

Ergotamine tartrate in large doses diminishes the acid secretory response to histamine and to a meal (Atkinson and Ivy, 1937–38)

Sulphonamides which are powerful inhibitors of carbonic anhydrase, have a small effect on secretion (Davenport, 1941)

Oil of peppermint applied locally has a depressing effect (Necheles, and Meyer 1934–35)

Irradiated ergosterol decreases gastric acidity in man in proportion to the amount of ergosterol used (Bauer, Marble Maddock and Wood, 1931)

Centrally acting *emetics* (apomorphine, apocodeine emetine, quinine) decrease the acid gastric secretion

Calcium bicarbonate and *aluminium hydroxide* preparations cause the greatest rise in pH and the greatest decrease in peptic activity (Steigmann and Marks 1943)

Calcium lactate and *calcium chloride* inhibit both the nervous and chemical type of secretion (Grant 1941a b)

Alkalis reduce but do not depress gastric secretion Absorption of sodium bicarbonate accelerates gastric evacuation and in normal therapeutic doses does not give a "rebound reaction (Stafforth 1953)

Severe artificial fever produced by the injection of bacterial products or by high environmental temperatures may practically abolish gastric secretion in dogs (Meyer, Cohen and Carlson 1918)

Implanting pedicle grafts of jejunum into the wall of the stomach shows that the normal responses to such secretory stimulants as histamine and alcohol (increased acidity of the gastric juice and lowered pH of the gastric mucosa) may be reversed or markedly diminished (Andrus Lord Stefko and Dingwall 1943–44) When portions of duodenum, jejunum ileum or colon are used for such implants the factor causing this alteration of gastric secretion is seen to be confined to the duodenum and jejunum (Lord Andrus and Stefko 1943)

Bridzius (1926) found that both walking and heavy exercise inhibit gastric secretion, and that the decrease is more marked after heavy exercise than after walking Crandall (1928) observed in Pavlov pouch dogs that heavy exercise markedly depressed the gastric secretion and that there is a considerable variation in the effect of the same amount of exercise in different animals

Hormonal control

Hormonal stimulation

GASTRIN

Pavlov and his pupils have shown in a conclusive manner that appetite is responsible for the initial flow of gastric juice following a meal but not for the sustained flow which continues for several hours afterwards

that water is a strong gastric stimulant but, according to Farrell (1928b), water does not stimulate the secretion of gastric juice by local action According to Kay (1947) ingestion of water inhibits gastric motility in normal subjects for 5 minutes (hot water has a similar but briefer effect) There is little evidence that water has a specific stimulating effect on the gastric glands, the results obtained by these authors appear to be due to a distension of the stomach which induces increased motility with consequent increase of secretion

GLANDULAR SECRETIONS

Insulin — This increases both gastric motility and secretions Necheles, Olson and Morris, (1941) stated that in dogs insulin may produce inhibition of both these gastric functions The effects of insulin hypoglycaemia on the digestive system are usually interpreted as being due to stimulation of vagus centres in the brain, particularly those of the hypothalamus (Jogi, Strom and Uvnas, 1949)

Pituitary extracts — The secretions of the posterior lobe of the pituitary gland produce vigorous contractions of the intestines, but apparently not of the human stomach (Necheles, Maskin, Strauss, Strauss and Taft, 1936, Van Dyke, 1936) Both pituitary extract and pitressin produce vasoconstriction and diminution of the blood flow through the stomach and, consequently, a relative anoxaemia

Liver — Kim and Ivy (1933) obtained vasodepressor free extracts of liver which contained potent secretagogues for gastric secretion Their observation that the action of the liver extract when administered by direct gastric lavage is four times stronger than when injected intravenously, has been confirmed by Butler, Hands and Ivy (1943)

TOBACCO

The majority of reports indicate an increase of acidity after a test meal (Ehrenfeld and Sturtevant, 1941) Nicotine stimulates gastric secretion

Chemical inhibition

HISTAMINE ANTAGONISTS

Histaminase, an enzyme which destroys histamine, can be extracted from various organs, especially from the kidney It may be concerned with the removal of histamine formed locally in an organ on reaching it in the circulation According to Wright (1945), however, histamine is non specific and acts as a de aminizing enzyme on a number of amines Histamine antagonists have little or no effect on gastric secretion (Sangster, Grossman and Ivy, 1946) but have a marked adrenergic potentiation (Yonkman, 1947)

Atropine and its derivatives act on the gastric musculature by blocking the effect of acetylcholine on the muscles, blood vessels and secretory cells In the presence of atropine, vagus stimulation still liberates acetylcholine, but the motor effects of the acetylcholine are either partially or completely suppressed (Klein, 1933) Small doses of atropine have been reported to increase

potent extracts are isolated from the pyloric mucosa, those from the upper duodenum are less active while extracts from the resting fundic mucosa have no effect on the gastric secretion

Uvnäs (1943) has shown that the gastric secretory excitant from the pyloric mucosa is not histamine and also (Uvnäs, 1945) that a protein like gastric secretory principle is found in the human pyloric mucosa Uvnas obtained a preparation of gastrin having a high degree of purity The active principle is a protein like water soluble substance *iso*-electrically precipitated at a pH of about 4–5 5

The observation that distension of the intestine will elicit secretion from a Heidenhain pouch or a transplanted gastric pouch suggests the possibility of an intestinal "gastrin (Beamer, Friedman, Thomas and Rehfuss, 1944, Uvnäs 1945)

Harper (1946) found that in the cat extracts of pyloric mucous membrane on intravenous injection stimulate the secretion of hydrochloric acid Extracts of the mucosa of the upper part of the small intestine also have some stimulative action, but extracts of the mucosa of the body of the stomach and the lower part of the small intestine are inactive The active material in these extracts does not dialyse through a Cellophane membrane and is destroyed by digestion with pepsin, they have no depressor action on the blood pressure of the cat and Gregory and Ivy (1941) failed to obtain a secretory response Grossman Robertson and Ivy (1948) found that distension of the pyloric portion of the stomach stimulates the secretion of hydrochloric acid by the fundic glands Since this effect occurs when all nervous connections between the subcutaneous transplantation and other parts of the stomach have been interrupted they consider this demonstration of the humoral transmission of the distension stimulus as conclusive evidence for the existence of a hormone for gastric secretion

Uvnäs (1942) and Kahlson (1948) believe that the stimulation of the vagus nerve to the stomach results in the release of gastrin and that neither the vagal nor the gastric mechanism can operate to its full extent in the absence of the other The gastrin response can operate in the complete absence of the vagus nerve as shown by the effects of secretagogues and distension in vagally denervated pouches (Harper and McKay, 1948) Furthermore Jemerin, Hollander and Weinstein (1943) showed that insulin hypoglycaemia or sham feeding produced strong vagal stimulation of the main stomach with high acid production, yet no secretory response occurred in the pouch Janowitz and Hollander (1951b) observed failure of vagally denervated gastric pouches to secrete acid in response to intense vagal stimulation of the stomach thus proving that vagal stimulation does not release gastrin

Dragstedt Woodward Storer Oberhelman and Smith (1950) who observed the effects of the gastric antrum *in situ* after exteriorization and transplantation concluded that the antral secretion accounts for the gastric phase of digestion, that it is highly specific in function and differs in this respect from that of the fundus or intestines Their data are in harmony with the view that the antrum is an internal secreting organ which elaborates a

The hypothesis of the humoral control of gastric secretion by the pyloric mucous membrane was originally postulated by Edkins (1906) He made extracts of the pyloric mucous membrane in boiling water or hydrochloric acid, 0 4 per cent, and found it contained an active principle which he called ' gastric secretin ' or "gastrin" Extracts of the fundic mucous membrane did not contain this substance He found that atropine did not diminish the reaction and that it was not a ferment, as boiling leads to an increase rather than a diminution of its properties These observations were confirmed by the experiments of Lim (1922–23b) which, however, were criticized by Ivy, Lim and McCarthy (1925)

Edkins and Tweedy (1909) observed that when they placed food substances either in the pylorus or in the duodenum, the fundus responded in all cases with marked secretion, if food substances were confined to the fundus region there was no evidence of any secretion whatever

Popielski (1920) agreed with Dale and Laidlaw (1910, 1911) that histamine was the active principle of all the glandular extracts which have a stimulative effect on gastric secretion which he described as "vasodilating' (Popielski, 1909)

Ivy and Farrell (1925), by their mothod of subcutaneous transplantation of the gastric pouch, observed that the humoral mechanism was concerned in the genesis of gastric secretion, this was confirmed by Lim, Loo and Liu (1927) Klein (1927) held that the major part of the gastrin secretion was initiated in the pylorus Klein and Arnheim (1932), who transplanted a gastric pouch into the subcutaneous tissue of the abdominal wall, observed that the pouch secreted acid and pepsin one hour after a meal Sacks, Ivy, Burgess and Vandolah (1932) suggested that histamine was the sole gastric excitant, a view also held by Priestley and Mann (1932), Gavin, McHenry and Wilson (1933), but not by Wilhelmj, Finegan and Hill (1937), and Gray (1937)

Klein (1935) found that the response of a subcutaneously transplanted fundic pouch to a meal was significantly reduced or was abolished by resection of the antrum of the main stomach These observations were confirmed by Woodward, Bigelow and Dragstedt (1948, 1950)

Ivy (1941) who investigated the action of secretagogues in dogs with a pouch of the entire stomach and with an autotransplanted pouch, or a ' two pouch ' dog, found that a humoral mechanism is involved in the action of secretagogues in the stomach since perfusion of the entire stomach pouch causes the transplant to secrete, but that a humoral mechanism was not involved in the action of mechanical distension

Komarov (1938a, 1942a), by boiling minced pyloric mucosa in a solu tion of 0 15 N hydrochloric acid, extracted a preparation which has a strong secretagogue effect on the fundic glands of the stomach It does not contain histamine or choline or other organic crystalloids Injected intravenously in cats it produces a gastric secretion of high acidity and low peptic power and is not affected by atropine It is a protein like body and has many chemical properties in common with secretin, but it is not identical with it The most

potent extracts are isolated from the pyloric mucosa, those from the upper duodenum are less active while extracts from the resting fundic mucosa have no effect on the gastric secretion

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powerful gastric stimulant (the gastrin of Edkins) when it comes in contact with food or products of digestion

GASTROZYMIN

It has been suggested that the secretion of pepsin is regulated by a hormonal mechanism Pratt (1940) injected crude secretin into cats and found that it stimulated pepsin secretion Bucher and Greengard (1942) and Babkin and Komarov (1944) showed, however, that highly purified secretin did not have this property, the pepsinogenic action being due to the pancreozymin (Wenger and Greengard, 1947) Grossman, Woolley and Ivy (1944) have shown that the pepsin concentration of gastric juice secreted by a transplanted fundic pouch was at the same level when stimulated by perfusion of liver extract through the main stomach as when stimulated by the injection of histamine, provided the volumes of secretion were comparable Uvnas (1945) reported that certain extracts of pyloric mucosa prepared according to his method for recovering gastrin caused an increase of pepsin concentration and that the pepsinogenic effect was not correlated with the acid stimulating potency He found (Uvnas, 1948b) a pepsinogenic principle in extracts from the pyloric and duodenal mucosa of cats, dogs and pigs and observed that the peptic cells are activated by mechanical stimulation of the pyloric mucosa

By a modification of the method of gastrin preparation described by Jorpes, Jalling and Mutt (1952) Blair, Harper, and Lake (1953) prepared extracts of pig's antral mucosa which do not affect the volume or enzyme content of pancreatic juice, have little effect on acid secretion, but stimulate pepsin secretion (gastrozymin)

DUOCRININ

This is the hormone which is released by the intestinal mucosa when certain foodstuffs are in contact with it and which stimulates the duodenal glands of Brunner to secrete (Florey and Harding, 1933, 1934, 1935, Fogelson and Bachrach, 1939–40, Wright, Jennings Florey and Lium 1940–41, Florey, Wright and Jennings, 1941) There is satisfactory evidence that parenteral injection of mucosal extracts acts as a powerful stimulant of Brunner's glands (Grossman, 1950)

Hormonal inhibition

ENTEROGASTRONE

It has long been recognized that the addition of one ounce of oil to an Ewald test meal markedly reduces the gastric secretory response Pavlov (1910) has shown that the effect of fat on the secretion of gastric juice is not limited to inhibition and that if the meal of fat be at all large secretion of gastric juice is resumed at the third hour, this late secretion lasts a long time and furnishes a considerable quantity of juice Fat produces inhibition of gastric secretion in a denervated Heidenhain pouch (Robins and Boyd, 1923), in a pouch of the entire stomach (Lim, Ivy and McCarthy, 1925a) and in

an auto-transplanted denervated gastric pouch (Farrell and Ivy, 1926, Lim, Loo and Liu, 1927, Feng, Hou and Lim, 1929)

Kosaka and Lim (1930) prepared an olive-oil extract of the upper part of the small intestine which, on intravenous or subcutaneous injection, inhibited gastric secretion, but similar extracts made from the gastric mucous membrane were without effect Kosaka, Lim, Ling and Liu (1932) prepared a trinitrophenol concentrate of the extract and suggested that it should be called 'enterogastrone' Gray, Bradley and Ivy (1937) further purified enterogastrone Kosaka and Lim (1933) using the trinitrophenol preparation intravenously found that gastric motility was inhibited in dogs with gastric fistulae but that the action of this preparation did not approximate the inhibition produced by oil given by mouth Lim (1933) postulated that one chalone is responsible for the inhibition of both gastric secretion and gastric motility by fat

Quigley (1934) found that in dogs whose stomachs were denervated by sectioning the extrinsic nerves (double vagotomy, double splanchnicotomy and coeliac ganglionectomy), the introduction of fats and carbohydrates into the stomach led to gastric inhibition similar to that occurring in the normal stomach Fats and carbohydrates in the auto-transplanted pouch did not inhibit motility of the pouch or the main stomach, even when the pylorus was obstructed On the other hand, a pouch of the entire stomach was inhibited by fats or carbohydrates introduced into the duodenum even when the blood vessels of the stomach had been stripped and phenolized and even when the pylorus was obstructed Quigley, Zettelman and Ivy (1934) concluded that the nature of the humoral agent which causes the inhibition of the motility of the extrinsically denervated gastric tissue (auto-transplanted pouch, denervated pouch of the entire stomach and the vagotomized splanchnicotomized coeliac ganglionectomized stomach) is not established unequivocally by their observations They made the significant deduction that since fat in the upper intestine tends to decrease gastric motility and evacuation but increases intestinal motility, a mechanism is provided to prevent accumulation of fat in the upper intestine (a region particularly sensitive to its presence) Abnormalities of this mechanism may occasion the nausea eructation regurgitation and vomiting which sometimes follow fat ingestion Fat introduced into the jejunum of dogs by jejunal fistula (Waugh 1936) produced marked atony of the whole stomach

The inhibition of gastric secretion and motility by the introduction of neutral fat (olive oil), fatty acid or sodium oleate into the duodenum was demonstrated by Shay, Gershon Cohen and Fels (1939) in experiments performed on human subjects Card (1941) found that the fatty acids were more effective than the corresponding fats and that there was a linear relationship between the dose of fatty acid used and the mean duration of inhibition obtained There was no correlation between the effectiveness of the oil used and its saponification or iodine value Tidwell and Cameron (1942) have suggested that the inhibitory mechanism varies with the chemical composition of the fat ingested That inhibition of pepsin was not due to

powerful gastric stimulant (the gastrin of Edkins) when it comes in contact with food or products of digestion

GASTROZYMIN

It has been suggested that the secretion of pepsin is regulated by a hormonal mechanism Pratt (1940) injected crude secretin into cats and found that it stimulated pepsin secretion Bucher and Greengard (1942) and Babkin and Komarov (1944) showed, however, that highly purified secretin did not have this property, the pepsinogenic action being due to the pancreozymin (Wenger and Greengard, 1947) Grossman, Woolley and Ivy (1944) have shown that the pepsin concentration of gastric juice secreted by a transplanted fundic pouch was at the same level when stimulated by perfusion of liver extract through the main stomach as when stimulated by the injection of histamine, provided the volumes of secretion were comparable Uvnas (1945) reported that certain extracts of pyloric mucosa prepared according to his method for recovering gastrin caused an increase of pepsin concentration and that the pepsinogenic effect was not correlated with the acid stimulating potency He found (Uvnas, 1948b) a pepsinogenic principle in extracts from the pyloric and duodenal mucosa of cats, dogs and pigs and observed that the peptic cells are activated by mechanical stimulation of the pyloric mucosa

By a modification of the method of gastrin preparation described by Jorpes, Jalling and Mutt (1952), Blair, Harper, and Lake (1953) prepared extracts of pig's antral mucosa which do not affect the volume or enzyme content of pancreatic juice, have little effect on acid secretion, but stimulate pepsin secretion (gastrozymin)

DUOCRININ

This is the hormone which is released by the intestinal mucosa when certain foodstuffs are in contact with it and which stimulates the duodenal glands of Brünner to secrete (Florey and Harding 1933, 1934, 1935, Fogelson and Bachrach, 1939–40, Wright, Jennings, Florey and Lium 1940–41, Florey, Wright and Jennings, 1941) There is satisfactory evidence that parenteral injection of mucosal extracts acts as a powerful stimulant of Brünner s glands (Grossman 1950)

Hormonal inhibition

ENTEROGASTRONE

It has long been recognized that the addition of one ounce of oil to an Ewald test meal markedly reduces the gastric secretory response Pavlov (1910) has shown that the effect of fat on the secretion of gastric juice is not limited to inhibition and that if the meal of fat be at all large, secretion of gastric juice is resumed at the third hour, this late secretion lasts a long time and furnishes a considerable quantity of juice Fat produces inhibition of gastric secretion in a denervated Heidenhain pouch (Robins and Boyd, 1923), in a pouch of the entire stomach (Lim, Ivy and McCarthy, 1925a), and in

Morlock (1948) observed in 20 human volunteers that 200 mg intramuscularly did not affect the gastric secretory response in 10 volunteers during a double histamine test, 100 mg administered intravenously to dogs with Heidenhain pouches inhibited the output of acid but mild to severe toxic reactions occurred with some rise of temperature, salivation, retching weakness and even collapse Failure of inhibition of gastric secretion by enterogastrone preparations was also observed by Uvnäs (1948a), Benditt, Kirsner and Rowley (1949), Benditt and Rowley (1949), Segal, Ellis and Watson (1950), Wollum and Pollard (1951) Bone Cassel, Ruffin and Reeves (1951) warned that it should be used with caution in man

ANTHELONE

Reference may be made here to anthelone (Sandweiss, 1943) which is the principle extractable from small intestinal mucosa (entero-anthelone) and from urine (uro-anthelone) which exerts an anti ulcer effect in Mann Williamson dogs and is not due to the gastric secretory depressant activity (urogastrone and enterogastrone) Its hormonal status is uncertain Grossman (1950) draws attention to the fact that anthelone has not been chemically separated and is prepared in the same manner as urogastrone or enterogastrone, the possibility that a single substance in each of these extracts is responsible for these two kinds of activity must also be borne in mind

URO-ANTHELONE

Sandweiss Saltzstein and Farbman (1938) tried various endocrine preparations on Mann Williamson dogs, they found that chorionic gonadotropin, prepared from the urine of pregnant human subjects, was the only one which reduced the incidence of ulcers Broad and Berman (1941) confirmed their results but Sandweiss, Saltzstein and Farbman (1939) Sandweiss and Friedman (1940) Sandweiss, Sugarman, Friedman Saltzstein and Farbman (1941) and Sandweiss and Saltzstein (1949) observed that urine from non pregnant women (and, therefore, devoid of chorionic gonadotropin) also exerted this beneficial effect, whereas urine from normal men was less effective and that from patients with peptic ulcer was ineffective

Grossman (1950) pointed out that statistical analysis of Sandweiss data revealed that the difference between the rates of effectiveness of urine extracts from pregnant and non pregnant females was not statistically significant, nor was that between urine extracts from normal men and male peptic ulcer patients The difference between urine extracts from females (pregnant and non pregnant) and males (with or without ulcers) was, however highly significant. The report that extracts of urine from patients with peptic ulcer inhibited gastric secretion (Friedman Recknagel, Sandweiss and Patterson, (1939), but did not protect against Mann Williamson ulcers (Sandweiss and Saltzstein 1949) was taken as evidence that urogastrone was present and uro-anthelone was absent thus favouring the view that they were separate substances Gray Culmer, Wells and Wieczorowski (1941) however showed that in peptic ulcer patients urogastrone is reduced below

enterogastrone and is a nervous phenomenon because it fails to occur after vagotomy was shown by Grossman, Greengard, Woolley and Ivy (1944) They argued that it might be anticipated that the inhibition of pepsin secretion by fat is also accompanied by a humoral or hormonal mechanism

Retardation of gastric evacuation in the human by the presence of fat in the stomach was shown by Annegers and Ivy (1947) and by the presence of fat in the intestine by Harris, Grossman and Ivy (1947)

Morris, Grossman and Ivy (1947) found that the motor inhibitory factors in enterogastrone and urogastrone are active only in the vagally innervated stomachs

The oral route is ineffective in dogs (Gray, Bradley and Ivy, 1937), and in the human (Saltzstein, Sandweiss, Hammer, Hill and Vandenberg, 1947a, Pollard, Block, Bachrach and Mason, 1948, Sandweiss and Saltzstein, 1949, Gambill, Morlock, Butt, Wollager and Code, 1950)

It may be noted that while Ivy (1941) believed that gastric stimulants may be extracted from practically all tissues of the body, Sandweiss, Sugarman and Lockwood (1948) suggested that even enterogastrone may contain a secretory stimulant also

THERAPEUTIC ADMINISTRATION OF ENTEROGASTRONE

Hands, Greengard, Preston, Fauley and Ivy (1942) claimed that enterogastrone produced immunity in Mann Williamson dogs against jejunal ulcer, an observation which was confirmed by several authors but not by Pollard, Wollum and Green (1950) Ivy (1945) believed that if enterogastrone therapy did not prove to be clinically effective, it could only be concluded that the ulcer which develops in the Mann-Williamson dog is aetiologically quite different from that which occurs in man and that current opinion and evidence was decisively contrary to such a conclusion Gray, Grossman and Robinson (1945) could not prevent gizzard erosion in chicks, and Grossman, Dutton and Ivy (1946) histamine induced ulcers by daily injections of enterogastrone concentrate, it did not afford protection against rumenal ulcers which form in rats following pyloric ligation (Morris, Grossman and Ivy, 1947a, b) Levin, Kirsner and Palmer (1948a) found that enterogastrone concentrate did not significantly affect the secretory response of the human stomach to histamine or insulin Hands Greengard, Preston, Fauley and Ivy (1942) claimed that only 6 out of 25 Mann-Williamson dogs developed jejunal ulcer during a one year period of treatment, but Sandweiss and Saltzstein (1949) and Visscher and Lyster (1949) who used extracts from the same commercial source could not confirm the results

Sandweiss, Sugarman and Lockwood (1948) found that of 27 patients who were treated parenterally with enterogastrone, 14 became symptom free, 3 were moderately improved, and 10 failed to obtain any symptomatic relief Haemorrhage developed in 3 patients whilst they were regularly receiving injections Total relapse within one year affected 70 per cent of the cases, the injections were painful, 2 cases developed urticaria Ferayorni, Code and

Treatment with urinary extracts failed to protect against the occurrence of peptic ulcer in dogs receiving cinchophen (Farbman, Sandweiss and Saltzstein, 1939, Slutzki, Wilhelmj and Stonor, 1941)

According to Kaulbersz, Patterson Sandweiss and Saltzstein (1947) the pituitary gland plays a part in the formation or excretion of urogastrone

Patterson, Kaulbersz, Sandweiss and Saltzstein (1949) found that extracts of urine of hypophysectomized dogs did not exhibit the prompt inhibitory effect which is characteristic of urogastrone prepared from normal urine In small doses it produced an increase of secretion in response to histamine and in larger doses a strong delayed inhibition, showing that it contains both stimulatory and inhibitory agents

Sandweiss and Saltzstein (1949) observed that extracts obtained from human urine (pregnant women normal women and normal men) were of definite benefit when administered orally to Mann Williamson dogs Extracts obtained from ulcer patients had some, but very much less, activity Pregnancy urine extract administered orally did not prolong the life of the animals but it did stimulate epithelization in a significant number of the ulcers The gonadotropic hormone from pregnant mare s serum was definitely beneficial Progesterone stimulated epithelization, theelin was of no value, post pituitary extract produced no effect Enterogastrone administered orally produced some benefit, but when it was administered parenterally the concentrate employed had no effect

Grossman (1950) expressed the opinion that from the evidence at hand no definite conclusion can be reached whether urogastrone represents an excretory product of enterogastrone and considers its hormonal status as uncertain

Conclusions

The production of enterogastrone by the presence of fat in the upper intestine cannot be considered as an exceptional phenomenon because the inhibitory effect produced by fat is also produced by a large group of amino acids when introduced into the small intestine It has been shown that the introduction of hydrochloric acid into the duodenum produces an inhibition of gastric peristalsis which is much too prompt to be interpreted as being due to a humoral mechanism alone Distension of the duodenum or other parts of the small intestine will cause gastric inhibition Nevertheless, it must be recognised that the effect produced by enterogastrone is sufficiently marked to give it special significance

The isolation of gastrin as a specific stimulus to gastric secretion calls forth the existence of a specific inhibitor for the maintenance of the physiological equilibrium by the antagonistic action of these stimuli The failure to isolate the inhibitory substance which follows protein digestion does not exclude the possibility of its existence That some such mechanism may be involved was indicated by Babkin (1944) who suggested that the mechanism of the inhibitory action of hydrochloric acid in the duodenum on the process of formation of the gastric juice may be due to a chalone which is found in the

normal, and re examination of Sandweiss' data revealed that anthelone activity was not entirely absent from the urine of these patients, this evidence favours the view that urogastrone and uro anthelone are identical substances

Tests on the Shay rat have shown that the intestinal and urinary extracts which may inhibit the formation of these ulcers accomplish this by depressing gastric acid secretion (Risley, Raymond and Barnes, 1947)

Sandweiss (1951) emphasized that the anthelones have not yet been chemically separated from enterogastrone or urogastrone

UROGASTRONE

Sandweiss, Saltzstein and Farbman (1938) first reported that an extract from the urine of pregnant women—Antuitrin S—has a prophylactic and therapeutic effect on experimental ulcers in dogs produced by the Mann-Williamson technique of surgical duodenal drainage and further noted that an extract from urine of normal women had a similar effect (Sandweiss, Saltzstein and Farbman, 1939)

Necheles, Hanke and Fantl (1939) extracted a preparation from normal human urine which produced an inhibitor effect on gastric secretion and motility which they called "urogastrone" These observations were confirmed by Gray, Wieczorowski and Ivy (1939) and by Culmer, Atkinson and Ivy (1939) Urogastrone resembles enterogastrone in both chemical and physiological behaviour (Culmer, Gray, Adkison and Ivy, 1940) Gray (1941) argued that if urogastrone is in fact excreted enterogastrone, the feeding of fat should augment the output in the urine It has been found that the output is actually greater after the ingestion of a fatty meal than during fasting, but the same effect is obtained after the ingestion of a fat free meal Schiffrin and Gray (1942) observed that the intravenous administration of 1 mgm of urogastrone effectively inhibited the volume of gastric secretion and the output of free acid in enterectomized dogs and in total gastric pouches of vagotomized dogs Wieczorowski, Gray, Culmer and Wells (1941) observed that the apparent excretion of urogastrone is decreased by removal of the small intestine and increased by the induction of diuresis, by the ingestion of a high or low fat diet and by the exclusion of digestive secretions from the small intestine They do not support the view that urogastrone and enterogastrone are identical

Inhibitory effects of extracts of urine were reported from pernicious anaemia and gastric cancer patients (Friedman Recknagel Sandweiss and Patterson 1939) from normal dogs (Gray Wieczorowski and Ivy, 1939) from gastrectomized and duodenectomized dogs (Friedman Saltzstein and Farbman, 1940), and in the achlorhydric gastric juice in patients with carcinoma of the stomach (Brunschwig Clarke, Van Prohaska and Schmitz 1940) It was absent from the urine of ulcer patients (Saltzstein and Farbman, 1939) but present in the human female (Capps and Patterson, 1941) Bourque, Friedman, Patterson and Sandweiss (1943) observed that the intravenous injection of urine extracts of duodenal ulcer patients and normal human males inhibited the gastric motility of dogs with gastric fistulae

neutralization or dilution by alkaline or neutral secretions of other cellular groups Gastric secretion at its height has little if any, variation in its acidity and its concentration of total and neutral chlorides, but at the very beginning and at the very end of the secretory period the total chlorides are somewhat lower *while the proportion of the neutral chlorides is higher* Several theories have been advanced to explain these changes

Pavlov (1898), following Heidenhain (1883), suggested that the gastric juice issuing from the glands has a constant acidity and that the variations in the acidity of the gastric contents at the beginning and at the end of the secretory period are caused by its partial neutralization by the alkaline mucus of the stomach At the beginning of the secretory period a large amount of mucus is available which, therefore reduces the acid concentration At the end of the secretory period when the volume of the acid secretion is greatly diminished, the time factor allows for the reduction of the acidity

Rosemann (1907) suggested that the variations of the gastric juice are independent of the alkaline surface epithelium mucus and that the total chloride concentration is practically constant. He believed that two processes take place simultaneously namely the accumulation of neutral chloride in the gastric mucosa, and the formation of hydrochloric acid and that therefore the secretory cells have the double function of (1) concentrating chloride to a higher level than that of the chloride in the blood and (2) *combining the* Cl ion with the H ion to form hydrochloric acid At the end of the secretory period the acidity of the gastric juice is diminished and the concentration of neutral chloride is increased whereas the total chloride concentration remains practically constant. Rosemann ascribed the presence of cations in gastric juice to incomplete conversion of neutral chlorides to hydrochloric acid in the parietal cells This view was supported by Forster and Lambert (1908)

Boldyreff (1904 1914) suggested that an important factor in lowering the acidity of gastric juice from that actually secreted by the gland (0 5 per cent) to that usually found in the cavity of the stomach (0 25 per cent) is the entrance of the alkaline intestinal contents (pancreatic juice, bile and succus entericus) into the stomach and that this usually occurs when the acid in the stomach rises much above 0·25 per cent Similar views were held by Spencer Meyer Rehfuss and Hawk (1915) Rehfuss and Hawk (1920) Moppert (1921) Jarno and Vandorfy (1921) Burget and Steinberg (1922), and Stewart and Boldyreff (1932) This mechanism which involves the function of the *pyloric sphincter is discussed in the chapter which deals specifically* with this subject

Baird, Campbell and Hern (1924a) pointed out that under normal conditions the chloride curve continues to rise when the acid curve is falling or has become level and that this must be due to neutralization by alkali the pyloric part of the stomach usually constituting the main factor in this neutralization although in some cases duodenal regurgitation may be more important

Roberts (1927) agreed with Katsch (1924) that the chloride secretion was independent of that of acid

intestine when acid comes into contact with the mucous membrane While urogastrone may not be identical with enterogastrone, it is possible that it may be its excretion product, or perhaps correspond to the production of an inhibitory agent following protein digestion in the upper intestine

Enterogastrone extracts that have so far been prepared inhibit gastric motility only in the vagally innervated stomach and, therefore, cannot be considered to contain the true hormonal substance and, according to Grossman (1950), there is nothing to suggest a physiological function for this inhibitor

The normal reduction of gastric acidity

Normal reduction of gastric acidity takes place in several ways The most important is that the acid glands cease to secrete at the end of normal digestion During prolonged fasting the gastric acidity was lower than the control when the control was approximately normal for the subject and it was higher when the control was abnormally low Immediately after fasting the acidity is higher than immediately before fasting (Hoelzel, 1926)

Robinson (1935) observed that when an intestine was filled with solution from the bile duct to the ileocaecal valve and tied off into segments, the contents of each segment assumed a *p*H characteristic of that section of the gut The *p*H increased from the bile duct to the caecum It is 6 5 in the duodenum to about *p*H 7 5 or 8 in the caecum There exists a definite physiological control mechanism for regulating the reaction of intestinal contents

In the absence of conditioned alimentary reflexes or in the absence of food from the gastro intestinal tract of healthy animals the gastric glands secrete alkaline mucus only and not acid (Babkin, 1932)

According to Bockus (1943) the real causes of a gradual decline in the acid curve are negative, not positive The various secretagogic factors responsible for the acceleration of flow of gastric juice after eating probably disappear from the circulation The stimuli which were originally responsible for nervous and hormonal effects on the gastric glands are no longer active

During the absence of secretory stimuli the parietal cells practically cease to secrete and the activity of the peptic and mucoid cells is reduced to a minimum, whereas the surface epithelium cells secrete mucus continuously (Babkin, 1944) Whether in man the secretion of acid is spontaneous or intermittent is not yet settled because many external factors may be involved which cannot be excluded (Babkin, 1950)

The regulation of the gastric secretory curve

Since acid is an element in the pathogenesis of chronic peptic ulcer it will be necessary to investigate the causes of the variations of the acid concentrations during the normal secretory period in order to establish the significance of their pathological deviations

It is now recognized that the parietal secretion possesses a constant acidity and that the variation of the concentration must be dependent on either

neutralization or dilution by alkaline or neutral secretions of other cellular groups Gastric secretion at its height has little if any variation in its acidity and its concentration of total and neutral chlorides, but at the very beginning and at the very end of the secretory period the total chlorides are somewhat lower while the proportion of the neutral chlorides is higher Several theories have been advanced to explain these changes

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MacLean and Griffiths (1928a, b) and MacLean, Griffiths and Williams (1928) have shown that during digestion the rise of acidity of the stomach contents ultimately attains the value at which it arrests HCl production, thus automatically exerting a control over the acidity of the secreted juice The concentration of total chloride in the gastric juice remains constant during the whole secretory period, but the concentration of hydrochloric acid is inversely proportional to the neutral chloride At first the acid preponderates because most of the chloride is secreted as hydrochloric acid and only a small part of it as neutral chloride Towards the end of the secretory period, however, more and more chloride is secreted in the form of neutral chloride and less in the form of hydrochloric acid until the gastric secretion contains practically no hydrochloric acid The fall in the high concentration is brought about not by the regurgitation of alkaline duodenal juices, but by dilution with a neutral fluid which contains neutral chloride and is secreted

Peptic activity of the gastric juice increases or decreases *pari passu* with the neutral chloride concentration (MacLean, Griffiths and Hughes 1929)

Hollander (1931) explained that the failure of these two opposing groups to agree appears to arise to a great extent from a difference in interpretation of the findings In any sample of mixed gastric juice the sum of the concentrations of total base (B+) and total acid (H+) will be equal to the sum of the concentrations of chloride (Cl–) and buffer anion (BUF–) The major part of the buffer containing fluid arises as an independent secretion of which the source is the neck chief cells of the gastric tubules and plays a major role as an intragastric agent in the normal control of gastric acidity

According to Goldberg (1932) intragastric regulation of acidity is brought about by three factors (1) reduction of the concentration of secreted hydrochloric acid when intragastric acidity has reached a certain level, and as its corollary (2) secretion of neutral chloride by the stomach, which plays a rather minor part by dilution, and (3) a combination of gastric mucin or an unknown substance with free acid The buffering of the secretions of the pyloric segment was found to be somewhat better than that of the fundus

Bolton and Goodhart (1931, 1933, 1936) found that when any substantial reduction in acidity of the gastric juice occurs the percentage of total chloride falls, showing neutralization and dilution by mucus and not replacement of acid by neutral chloride They believed that the means possessed by the normal stomach whereby it is able to reduce the acidity of its contents is the secretion of mucus and by two additional intragastric factors the rate of emptying of the stomach and most important of all, the cessation of secretion of gastric juice When the juice is secreted into the isolated stomach in very small amounts, such as may be seen at the end of a meal or in some fasting stomachs its acidity falls by neutralization with mucus inversely as the rate of secretion and remains constantly at this level if the rate of secretion is constant they believed that duodenal regurgitation was responsible for the regulation of gastric acidity

Teorell (1933 1939, 1940) adopted a physico-chemical view which suggested a "diffusion theory , hydrochloric acid diffuses steadily out of the

stomach contents into the mucosal cells or the blood and is exchanged against alkali chlorides (neutral chlorides) which diffuse in the opposite direction and thus a continuous process of ionic interdiffusion or exchange diffusion proceeds in the stomach

Ihre (1939) observed that in addition to a mucous secretion which has a buffering action there is also an acid reducing process which does not involve a change in the volume of the gastric juice, and he suggested that diffusion processes are responsible He also confirmed that the duodenal reflux is only exceptionally the factor

Apperly and Carey (1936) stated that when hydrochloric acid is introduced into the human stomach it is found that (*a*) the acidity is reduced, chiefly by dilution and only to a small extent by neutralization (*b*) the rate of reduction of acidity varies directly with the rate at which the stomach empties, and (*c*) the rate of reduction of acidity varies inversely as the concentration of neutral chloride and alkali in the fluids which dilute the gastric contents

Griffiths (1936) who introduced acid into the duodenum during the secretory activity of the stomach and also during fasting observed a considerable increase of neutral chloride and peptic activity and an arrest of the secretion of hydrochloric acid He therefore suggested that the entry into the duodenum of the acid contents of the stomach is an important factor in the regulation of gastric acidity

According to Pincus, Thomas and Rehfuss (1942) the depression of gastric secretion occurs only when the duodenal *p*H has fallen to approximately 2 5 This mechanism is brought into play when the acidity of the intestinal contents reaches levels which may be harmful to the intestinal mucosa (Pincus, Friedman Thomas and Rehfuss 1944)

Gray Bucher and Harman (1941) observed in dogs with vagotomized pouches of the entire stomach, that as the volume rate of secretion increases the *outputs* of total acid and neutral chlorides all increase in linear manner but at different rates but the *concentrations* of total and acid chlorides increase in a hyperbolic fashion while the concentration of neutral chloride decreases in a hyperbolic fashion As the acidity of the gastric juice increases the total chloride concentration increases and the neutral concentration decreases both in a linear fashion The acidity of the gastric juice varies directly with the total chloride concentration and inversely with the neutral chloride concentration

Shay, Gershon Cohen and Fels (1942) considered that hydrochloric acid of the gastric juice in man acts as 'a self regulator of its own secretion when it comes into contact with the mucosa of the duodenum They showed in normal subjects that the acidity of the gastric contents after an Ewald test meal was markedly diminished when 0 06 N or 0 072 N hydrochloric acid was dripped into the duodenum

Rehm (1944) attempted to reconcile the conflicting reports in the literature on the relationship between gastric secretion and potential and found that application of hydrochloric acid solutions to the secreting stomach and subsequent replacement with saline, resulted in a marked decrease in the

potential, and that this decrease in the potential was associated with a decrease in the secretory rate

Babkin (1944) rejected the observations of MacLean, Griffiths and Williams (1928) that the peptic activity of the gastric juice increases or decreases *pari passu* with the neutral chloride concentration, that is to say, the peptic activity is always associated with neutral chloride in the gastric secretion He believed that the existence of neutral chloride in the gastric juice and the variations in its concentration are regulated by some mechanism other than that which governs the secretion of pepsin

According to Teorell (1947), the problem of variations of concentration of electrolytes of the mammalian gastric juice can be regarded as a case of electrolyte diffusion across the stomach mucosa, which acts as a "dialysing membrane" for hydrochloric acid and alkali chloride He confirmed experimentally his simplified theory for interdiffussion of two binary electrolytes of the stomach blood system, and he deduced as consequences of his theory that, for a given case, variations of acidity, base and total chloride concentrations are functions of the secretion rate only, the acidity and total chlorides should increase, the base decrease with the rate of secretion

Horstmann (1947) observed a strong parallelism in the acidity and chloride in fasting juice as well as in secretion following stimulation by insulin, the graphic relation being very nearly rectilinear

In conclusion it may be stated that the present day consensus of opinion appears to be that regurgitation of the duodenal secretions into the stomach does not participate in the regulation of the gastric secretory curve

Gastric secretion in the newborn

Friedman (1942) stated that it is fairly well established that the stomach of the human foetus is potentially capable of secreting acid by the fifth month Parietal cells become distinguishable towards the end of the fourth month and presumably acid can be secreted after this time The literature is replete with reports on the presence of acid in the stomach of the premature and normally delivered unfed newborn infant Friedman (1942) quotes Ritter (1941) who made gastric analyses on 36 newborn infants ranging in age from half an hour to 14 hours With one exception, none of the infants had ever received any water or milk before the study was made The concentration of free acid in the fasting contents of the unfed newborn was high, over 50 per cent had more than 20 c c of $\frac{1}{10}$ N hydrochloric acid per 100 c c of gastric juice The free acidity ranged from zero to 56 units, the total from 11 to 84 units and the *p*H from 1 28 to 4 59 No free acid was recovered in the fasting stage in 4 cases In the premature and the full term newborn, gastric hunger contractions occur more frequently and are more persistent and more vigorous than in older babies (Carlson and Ginsberg, 1915, Taylor 1917) According to Davidson (1921), the motility of stomachs in infancy increases or diminishes as the gastric acidity rises or falls

In guinea pigs there may be a spontaneous secretion of acid gastric juice during late intra uterine life In dogs and cats there appears to be no spon

taneous gastric juice secretion *in utero*, but there is some secretory response to 'gastrin' when the foetuses are within a few days of term (Sutherland, 1921c)

Manville and Lloyd (1932) determined the *p*H of the gastric contents of 43 rat foetuses covering the last 5 days of gestation and showed that during this period the acidity reaches a maximum on the seventeenth day and thereafter declines Similar observations made on the gastric juice of 120 lactating rats covering the entire 21 days of the lactation period show five noteworthy features (*a*) there is a marked increase in acidity of the gastric juice as soon as the animal is born, (*b*) during the first week of lactation there is a gradual increase in acidity, (*c*) the middle third of the lactating period shows a slight decrease in acidity, (*d*) the last third of lactation shows a sharper increase in acidity than the first week, (*e*) the acidity at the end of lactation is not as great as is found in the adult animal They believe that there is an association of the highest incidence in pre natal and post natal mortality with these changes observed in the gastric acidity

CHAPTER 3

CO-ORDINATION OF MOTOR AND SECRETORY FUNCTIONS OF THE STOMACH

The motor and secretory responses of the stomach will be studied in their phases of the interdigestive and digestive stomachs in order to establish their relationship

THE INTERDIGESTIVE PHASE

The Fasting Stomach

The intake of food is normally dependent on the metabolic needs of the body and is regulated by the sensations of appetite and hunger

Appetite and hunger (*"l'appetit vient en mangeant'*, Rabelais)

The terms appetite and hunger are frequently used synonymously, but they represent different aspects of the desire to eat Hunger may exist without appetite, that is, there may be a refusal to take repugnant food when hungry—and appetite may exist without hunger, that is, when there is a temptation to eat succulent food without being hungry

Goodall (1908) attempted an analysis of the psychic factors in appetite He defined appetite as a desire for food, a vague sensation entirely dependent upon hunger, referred to the stomach but originating in the tissues, generally as a result of a definite want in them This he called the primitive hunger factor In birds, some fishes and monkeys the visual factor has preference, in the dog, the olfactory factor is chiefly concerned, in adult man, it is taste The olfactory sensation in man appears more potent in inhibiting appetite than in producing or augmenting it

Sensations of hunger and appetite increase during the first two or three days of starvation and then decrease even to complete abolition There is complete absence of hunger after the fifth day (Luciani, 1911)

Appetite is augmented by tasting palatable foods—but hunger is inhibited by taking or chewing palatable foods It would seem that hunger has reached its biological end as a motor stimulus when the foods reach the mouth, and at that stage appetite takes the place of hunger as the guide to the quantity of foods to be ingested (Cannon and Lieb, 1911)

According to Carlson (1912) the contractions of the empty stomach give rise to the sensation of hunger or 'hunger pangs by stimulation of different nerve endings in the wall of the stomach and not by stimulation of nerve endings in the gastric mucosa

Osborne and Mendel (1918) stated that desire of a young animal for food is something more than the mere satisfaction of calorific needs Rats and mice make selections which as a rule, are advantageous nutritionally (Mitchell and Mendel, 1921) Richter, Holt and Barelare (1937, 1938) found that rats would select a diet adequate for normal growth and reproduction from a number of purified foodstuffs simultaneously and separately available

Taste or appetite may not be safe guides in nutrition (Hoelzel and Kleitman, 1927)

Meyer and Carlson (1917) and Sleeth and Van Liere (1937) observed a depressing effect on appetite due to high environmental temperatures

According to Patterson (1933) the complex sensations that urge man and the higher animals to the ingestion of food are called hunger and appetite these two sensations are very intimately interrelated According to one view, appetite is the first degree of hunger it is associated with a desire to eat and is mild pleasant and agreeable in character Hunger on the contrary, is the result of not satisfying appetite and is a more advanced condition, disagreeable unpleasant and even painful From this viewpoint appetite and hunger differ only quantitatively Appetite may exist long after hunger has been satisfied Three groups of theories have been advanced to explain the genesis of hunger and appetite (1) those of a *peripheral origin* involving the stimulation of sensory nerves chiefly in the digestive tract, (2) those of *central origin* involving a direct stimulation of a hypothetical hunger centre in the brain by the blood or by changes in the metabolism in the centre itself, (3) those of a *general sensation* involving a combination of both central and general peripheral factors of hunger

Richter and Hawkes (1940) observed that, in rats, ingestion of thiamine chloride stimulated the carbohydrate appetite ingestion of riboflavin the fat appetite and ingestion of the four vitamins—thiamine chloride riboflavin nicotinic acid and vitamin B_6—increased the carbohydrate appetite almost to normal and decreased the fat appetite to normal

Although flavour may play an important role in the determination of appetite it is operative only when the diets are reasonably complete it is entirely ineffective when deficiencies in the diet exist (Cowgill Deuel and Smith 1925)

According to Quigley (1942) appetite is a cerebral phenomenon a conditioned reflex developed largely on previous feeding experiences which caused the disappearance of the hunger distress and its replacement by the feeling of well being Appetite is also based on the agreeable smell the taste and the appearance of food on habit and many other factors and in general is a pleasant experience According to Richter (1942) it is the direct expression of internal organic states of need and he maintained that self selection or correction of diet induced by various hormonal or fluid balance disturbances are part of an automatic self correcting homeostatic mechanism independent of experience

According to Young (1944) the general state of the organism—chemical

and neural—determines food preferences A sense of smell plays a dominant role (Young, 1945) Habit is an effective factor in the selection of food (Young, 1946)

The observation that five milligrams of d amphetamine abolishes all hunger sensations, inhibits food intake in normal animals and inhibits sham feeding, and depresses food intake in the gastric denervated animal, indicates that the action is on the brain and, therefore, that the hunger sensation is central rather than peripheral in origin (Harris, Ivy and Searle, 1947)

Appetite or "desire to eat" appears, according to Ginsberg, Feldman and Necheles (1948) to be primarily a psychic phenomenon The appetite gastric juice is quantitatively related to food The sensations of hunger induced by insulin continue to occur after complete vagotomy in man Vagotomy abolishes the gastric hunger pang by abolishing the gastric hunger contractions, not by interrupting the sensory pathway (Grossman and Stein, 1948–49)

According to Janowitz and Grossman (1949) the problem of hunger and appetite is an analysis of the factors involved in the adjustment of the intake of required nutritional materials to bodily needs Hunger can be considered in terms of three superimposed aspects (1) the physiological aspects, which may range from biochemical determinants to homeostatic regularity mechanisms, (2) behavioural aspects, and (3) conscious aspects The hunger state has two manifestations (1) hunger behaviour, which is the motor activity independent of learning, and (2) hunger sensation, which is the mental correlative (the psychic adjunct) Appetite is the desire to eat and specific appetites are desires to eat specific foods According to Debrée, Mozziconacci and Alloiteau (1950) appetite is a psychic manifestation while hunger is a somatic manifestation, ordinarily not conditioned by a psychic activity although it may temporarily be inhibited by affective perturbations (emotions)

Disturbance of appetite

Green (1925) drew attention to a specific form of perverted appetite observed in cattle—"bovine osteophagia' This perversion of appetite or pica manifesting itself as an *allotriophagia* or habit of eating miscellaneous indigestible material is also observed in man in abnormal states of health Theiler, Green and Viljoen (quoted by Richter 1942–43) found that osteomalacia, so prevalent in South African cattle, was associated with a phosphorus deficiency in the soil and vegetations of the regions in which the disease was prevalent, and that such animals were confirmed bone eaters Richter (1942–43) has suggested the possibility that various phenomena, ordinarily spoken of as perverted appetites, such as coprophagy infantophagia, autophagia, placenta eating and bone eating, may be regarded as instances of self regulatory activities

The period of interdigestive or hunger motility

Hunger contractions

Carlson (1912) established that during the first twenty four hours after a meal, the empty stomach exhibits two types of rhythmic movements one

relatively feeble, but continuous with a constant rate of contractions of twenty seconds' duration, the other relatively strong contractions which may end in tetanus The individual contractions of the group rhythm and the stronger contractions of the continuous rhythm are recognized as hunger pains The rhythms of the empty stomach make their appearance whether the stomach mucosa is acid or alkaline in reaction, but strong acidity or strong alkalinity causes inhibition All the essential characteristics of the hunger contractions of the empty stomach are determined by the local gastric mechanisms and not the extrinsic nerves

Cannon and Washburn (1912) showed that the contractions of the empty stomach were related to the sensation of hunger The inhibition of the stomach activity and the cessation of the hunger pains run parallel (Cannon and Lieb 1911)

According to Carlson, Orr and McGrath (1914) the similarity between the hunger contractions of the main stomach and of the stomach pouch supports the view that these contractions are caused primarily by a gastric automatism and not by motor impulses via the vagi nerves When the muscularis and myenteric isthmus joining the main and the secondary stomachs is relatively narrow the two stomachs exhibit complete independence of the hunger contractions, even to the point of vigorous activity of the one during quiescence of the other This fact points to a local automatism as the primary factor rather than to the condition of the blood, as the character of the blood flowing to the main stomach and the stomach pouch is necessarily the same Hunger contractions of the empty stomach decrease with age (Patterson 1914)

According to Hoelzel (1927) hunger produces a general increase in irritability of the central nervous system and vasomotor instability Animals appear to experience hunger after extirpation or denervation of the stomach, and also after vagotomy, splanchnectomy and coeliac ganglionectomy He observed himself (reported by Carlson 1917–18b) during a fast which lasted 41 days and he found that satiety cannot be produced until all the elements of hunger indicated at any time are satisfied by the amount and kind of food craved That the stomach is not the sole element in the production of hunger has been shown by Wangensteen and Carlson (1931) who reported the occurrence of hunger sensations in a case of complete gastrectomy

Faradic stimulation of the stomach and duodenum produces localized epigastric pain (Boyden and Rigler 1934) Hunger contractions occurring in the completely denervated stomach are strikingly similar in the transplanted gastric pouches and the main stomach from which they are made (Quigley Zettelman and Ivy 1934)

That hunger is not due to a general bodily state is shown by the fact that it is aroused while the intestine still contains plenty of unabsorbed food and becomes less intense in prolonged periods of starvation Filling the stomach with bulky material which possesses little nutritive value or is totally inedible, inhibits contractions characteristic of the empty organ and relieves the pangs of hunger it may even create a feeling of satisfaction

In the active stomach, sham feeding abolishes tonus waves In the inactive stomach, sham feeding results in the initiation of motor activity and in an increase in tonus (Lorber, Komarov and Shay, 1949)

There appears to be no explanation for the fact that whereas hunger contractions initiate disagreeable sensations, digestive contractions, which appear to be similar in nature, do not do so

The inhibition of hunger contractions

Motor inhibition of the gastro intestinal tract is produced by laparotomy (Pal, 1890) Bayliss and Starling (1899) found that when the abdomen of a dog was opened in a warm bath of saline solution the intestines were collapsed and motionless Handling the intestine "produced reflex inhibition of the whole length of the intestine which was abolished by section of the extrinsic nerves of the gut This observation was confirmed by Cannon (1906) and Auer (1907)

Hunger contractions are inhibited most effectively by the ingestion of food and more transiently by the sight of food (oral inhibition), by smoking, by psychic disturbances or by a variety of stimuli, especially those involving pain from any part of the body but the hunger pain itself is an exception Carlson (1913) has shown that the duration of the inhibition depends upon the quantity of material introduced into the stomach and on the degree of the hunger contractions This inhibition persists after section of both splanchnic nerves but it is greater after section of both splanchnic and vagus nerves The inhibition is therefore primarily a local reflex The sensation of hunger by contractions of the empty stomach in man, (confirmed in dogs) is due to stimulation of different nerve endings in the walls of the stomach and not to stimulation of the nerve endings in the gastric mucosa The absence of food means absence of mechanical stimuli and cessation or diminution of the secretion of gastric juice, and hence a diminished acidity This inhibition is in part dependent on the central nervous system, the afferent nerves being the vagi The contractions of the empty stomach may also be inhibited by stimulation of the taste buds and by mechanical stimulation of the afferent nerve endings in the mouth caused by chewing indifferent substances

The movements of swallowing lead to a temporary inhibition of the tonus of the stomach ('receptive relaxation) The inhibition of the stomach activity and the cessation of hunger pains run parallel Movements of the stomach are greatly diminished or absent altogether when the health and vigour are in any way impaired (Carlson 1912–13) Brunemeier and Carlson (1914) observed that inhibition of gastric tonus and contractions followed stimulation of the intestinal mucosa with a glass rod Carlson (1915) corroborated Cannon (1906) by reporting that hunger contractions of the stomach could be inhibited via both extrinsic and intrinsic pathways when the intestinal mucosa was stimulated chemically or mechanically Experimental hyperglycaemia produced by intravenous injection of gluco e inhibits normal gastric hunger contractions (Bulatao and Carlson, 1924) it is also inhibited by the introduction of dextrose or cane sugar into the duodenum

as well as by subcutaneous injection of atropine or adrenaline (Quigley Johnson and Solomon, 1929)

Impulses from the urinary tract, rectum peritoneum and from certain skin areas reflexly diminish the tonus and movements of the small intestine in a fashion analogous to that of the stomach the splanchnics containing the efferent paths for these reflexes (King 1924, Mathur, Grindlay and Mann 1948) Similar effects are produced by distension of the colon (Pearcy and Van Liere 1926), of the rectum (Loew and Patterson 1935, Youmans and Meek, 1937), by anhydraemia (Rose and Stucky 1928), anoxaemia (Crisler, Van Liere and Booher 1932, Pickett and Van Liere, 1939, but not by Hellebrandt Brogdon and Hoopes 1935), anaemia (Van Liere, Sleeth and Northup, 1936), and amyl nitrite (Painter, Todd and Kuenzel 1939–40)

The stimulation of hunger contractions

THE EFFECT OF INSULIN

In insulin hypoglycaemia (in normal dogs) increase in gastric tonus and hunger contractions appear at a blood sugar concentration of 0 08–0 07 per cent (Bulatao and Carlson 1924) These experiments were confirmed by Mulinos (1927–28) in dogs and Quigley, Johnson and Solomon (1929) in normal human subjects The insulin response is completely inhibited by the subcutaneous injection of atropine (Quigley, Johnson and Solomon 1929, Quigley and Solomon, 1929–30) Insulin does not increase the gastric hunger contraction in vagotomized dogs (Quigley and Templeton, 1930b) and may therefore be used as a test of the integrity of the vagi Lalich Youmans and Meek (1937) confirmed that insulin in intact dogs augments gastric motility, after vagotomy the stimulation is replaced by inhibition

Grossman Cummins and Ivy (1947) suggested that since insulin causes augmentation of food intake both in normal dogs and in dogs with intrinsically denervated stomachs the insulin hypoglycaemia acts directly upon the brain to excite food taking activity

Relation of the hunger periods of the stomach and duodenum

Quigley and Solomon (1929–30) confirmed the observations of Ivy and Vloedman (1925) that the hunger periods of the stomach and duodenum are intimately related

The period of interdigestive or basal secretion

The period of interdigestive or basal secretion concerns the secretions which occur in the absence of food in the stomach According to Carlson (1916) normal human gastric juice (appetite secretion), when secreted above a certain minimum rate, shows a practically constant total acidity of nearly 0 5 per cent HCl or the same as the gastric juice in normal dogs The gastric juice secreted by the normal stomach at a low rate shows lower than normal acidity and total chloride The contents of the empty stomach and the continuous or hunger secretion have a uniformly lower acidity than the appetite juice The total acidity of the contents of the empty stomach is

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Effect of food on gastric evacuation

Best and Cohnheim (1910b), in observations on dogs with gastric fistula and severed oesophagus, found that gastric emptying depended entirely on the quantity of food in the stomach Evacuation of 0 9 per cent saline was quicker than that of water and still quicker than that of 2 per cent saline Heat did not appear to have any influence

Northrop (1945) found that the average gastric emptying time in young males was a little over 2 hours Birchall, Fenton and Pierce (1946) observed in rats that gastric emptying time and intestinal absorption were greater with large volumes than small volumes of equal concentration and with concentrated solutions when contrasted with diluted solutions of equal volume Similar results were observed by Fenton and Pierce (1947) when cereal starch was fed to rats That the vagi are not essential for the production of this effect was shown in Heidenhain pouches (Templeton and Quigley, 1929–30) and in vagotomized stomachs (Quigley and Hallaran, 1932)

The action of glucose on the emptying of the stomach varies according to the concentration both in the normal stomach and in stomachs following gastric operations (Johnson and Ravdin 1935), the rate of gastric discharge of glucose solutions decreases with time (Pierce Haege and Fenton, 1941–42), the inhibitory effect of a solution of glucose introduced into the duodenum is not specific since a similar effect is produced by a 5 per cent solution of sodium chloride (Shay, Gershon Cohen, Fels and Siplet, 1942)

That fat is not specific in retarding gastric emptying was demonstrated by Van Liere, Northup and Stickney (1946) who showed that the addition of 25 g of glucose to a test meal significantly delayed gastric emptying the delay of emptying increasing as the concentration of glucose Henschel Keys Sturgeon and Taylor (1947) replaced part of the test meal iso-calorically with fat or sugar No delay in emptying was seen even when fat accounted for 70 per cent of the calories of the test meal Hunt and Spurrell (1948) found that it was necessary to add 100 g of sucrose to a one pint test meal in order to cause a significant delay in emptying

Hunt and Macdonald (1954) observed that in man the larger the initial volume of the meal the greater was the initial rate of emptying

Proteins

The gastro-inhibitory effects of proteins and their acid digestion products when placed in the intestine are qualitatively similar and resemble the inhibitory effect of HCl (Thomas and Crider, 1939) *

Carbohydrates

Carbohydrates require but little gastric motility and secretion a 5 per cent solution of glucose produces very slight secretion and leaves the stomach

* According to Arrhenius (1909) the evacuation time of the stomach in dogs (fed on raw meat) is proportional to the square root of the amount of food ingested and the juice secreted $= K \sqrt{\text{amount of food ingested}}$ (K = 36 1)

about 0 2 per cent or less The acidity of the continuous or hunger secretion is higher and the greater the secretion rate the higher the acidity until it may equal that of the appetite juice In no instance does the acidity of the continued secretion exceed that of the appetite juice

In starvation, there is a continuous gastric secretion which shows apparently spontaneous periods of more rapid secretion Hoelzel (1926), who submitted himself to long periods of starvation, observed that during a fast of 40 days the acidity of the fasting gastric contents varied mainly in synchrony with the period of gastric motor activity It was relatively high on some days while it remained characteristically low on other days

Necheles (1949) thought that the interdigestive phase with little or no acid secretion exists in many persons during sleep but rarely during the day and that its occurrence may depend on diet and excitability of the secretory mechanism

The question of complete gastric secretory rest in day time in the human being is rather an academic one since thinking of food, swallowing of saliva and regurgitation of duodenal juices act as stimulants of gastric secretion Sensations of hunger do not appear immediately on awakening but are usually produced some time later following physical activity, small amounts of acid in the stomach do not usually give rise to hunger pains The contents of the human stomach after awakening may be due to night secretion which has been retained in the stomach or to some sudden onset of secretion

The volume of the gastric residue may vary within wide limits Carlson (1915a) found an average of 20 cc , Rehfuss, Bergeim and Hawk (1914a), Rehfuss and Hawk (1921), and Baird, Campbell and Hern (1924b) observed a range of a few cc to 180 cc in normal persons with an average of 50 cc

THE DIGESTIVE PHASE

The Regulation of the Motor Activity of the Digestive period

According to Grey (1917–18) the normal stomach possesses a striking capacity for adapting its size to the volume of its contents with only minimal changes in intragastric pressure This capacity disappears only shortly before the viscus ruptures As the rate of change in volume of contents increases, the extent of the postural activity decreases The extrinsic nerves are not directly concerned with the postural configuration of the viscus The mechanism responsible for these changes concerns solely the musculature itself together with the intrinsic nervous mechanism Soon after the stomach has become filled, peristaltic waves are seen to take their origin about the middle of the body of the viscus, and to course towards the pylorus The region above the origin of these waves—that is, the cardiac half of the body of the stomach and all the fundus (the cardiac pouch)—is free from peristaltic waves but is the seat of tonic contraction which as digestion proceeds presses steadily with increasing force upon the mass of food and delivers it slowly to the lower and more active portion of the stomach

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rapidly (Kalk, 1928) Carbohydrates entering the normal empty stomach inhibit hunger contractions and this phenomenon occurs in the denervated stomach and is definitely the result of a humoral factor (not carbohydrate *per se*) produced by the presence of carbohydrate in the upper intestine (Quigley and Phelps, 1934)

Fat

The observation that the presence of fat in the upper digestive tract decreases gastric motility was first made by Ewald and Boas (1886) and confirmed by Pavlov (1910) and his pupils Lintwarev (1903) demonstrated that fats limited to the intestine inhibited gastric motility Edelman (1906) and Carlson (1916) observed that fat decreased the motility of the fasting stomach Cannon (1911) observed roentgenologically that fats delayed gastric evacuation, which he ascribed to the effect of a reflex causing pylorospasm According to Lim (1933) fat inhibits gastric motility and both the nervous and chemical phases of gastric secretion, a nervous reflex not being essential in this action, but a chemical one (*see also* enterogastrone) The introduction of fatty acids or soaps into the proximal intestine of fasting dogs inhibits the motility of the pyloric antrum, sphincter and duodenal bulb in a manner qualitatively similar to that produced by natural fats (Quigley and Meschan, 1941) Cream in the duodenum inhibits the pyloric region and decreases or reverses the antral bulbar basal and phasic pressure gradients Fats retard gastric evacuation chiefly by decreasing antral propulsive peristalsis Sphincter spasm is not involved, on the contrary, evacuation is retarded in spite of sphincter relaxation (Quigley, Werle, Ligon, Read, Radzow and Meschan, 1941) The stomach empties very slowly after a large amount of fat (Morin and Monges 1951)

Proteins (Thomas and Crider, 1939), carbohydrates (Quigley and Phelps, 1934) and fats (Quigley, Zettelman and Ivy, 1934), that is the main constituents of food, all have a similar action on gastric motility and secretion, namely, one of inhibition which varies quantitatively according to the quality of the substance concerned

Effect of acid on gastric motility

Therapeutic doses of hydrochloric acid in the *stomach* exert little or no physiological action on the motor activities and the pressure changes in the pyloric sphincter region or on the process of gastric evacuation (Van Liere and Sleeth, 1940) Hydrochloric acid in the *duodenum* is moderately effective in suppressing the action of the pyloric antrum and this retards gastric evacuation The pyloric sphincter and the upper duodenum are also inhibited but this appears to be of slight importance in the evacuation process (Quigley Reid, Radzow Meschan and Werle 1942) Gastric motility was progressively inhibited as the intestinal pH fell from 3 0 to 2 0 and completely abolished at pH 2 0 There was no effect above pH 3 0 Gastric motility gastric secretion and gastric emptying are influenced in a parallel manner by acid in the intestine (Thomas 1947)

The presence of hydrochloric acid in the upper intestine produces inhibition of gastric motor activity (Boldyreff, 1904) Strong solutions of hydrochloric acid (0 24 to 0 53 per cent) added to a test meal produce noted delay of gastric evacuation Weaker solutions of HCl (0 09 to 0 23 per cent) prolong the evacuation time in achlorhydric patients only (Shay and Gershon Cohen, 1934) The threshold of gastric inhibition in the dog is below *p*H 3, whereas the maximum acidity of the mixed duodenal contents when on a diet of lean meat is near *p*H 3 6 or even higher when on a carbohydrate or a fat diet The regulation of gastric emptying depends not so much on the acidity of the chyme entering the duodenum as on the food substances themselves or the products of their digestion (Thomas and Crider, 1936, 1939)

Effect of alkali

Stewart and Boldyreff (1932) have shown that weak alkali leaves the stomach with the same rapidity as weak acid (no liquid leaves the stomach more rapidly than water) and that strong alkalis inhibit the emptying of the stomach as much as acids

Sodium bicarbonate decreases the emptying time of the stomach (Van Liere and Sleeth, 1940)

Influence of osmotic pressure

The observations of Apperly (1926) indicate that the osmotic pressure of the gastric contents is a factor influencing the emptying time of the stomach MacLeod, Magee and Purves (1930) found that hypertonic glucose solutions when fed to rats were reduced to isotonicity before evacuation, and McSwiney and Spurrell (1933b) observed that hypertonic meals delayed gastric evacuation proportionately to their hypertonicity According to Hunt, Macdonald and Spurrell (1951), the achievement of a certain intragastric osmotic pressure by dilution is not a necessary precursor of gastric emptying after the administration of pectin meals of high osmotic pressure

There is an interdependence of gastric secretion and CO_2 content of the plasma (Apperly and Crabtree, 1931, Browne and Vineberg 1932) Anoxia in dogs (Van Liere, Crisler and Robinson 1933 Stickney and Van Liere 1942) and in human subjects (Van Liere, Lough and Sleeth, 1936) and severe anaemia (Jacobson and Palmer 1943) delay gastric emptying

The effect of heat and cold

Slight elevations of body temperature do not affect gastric motility whereas considerable elevations will depress it Fever (Meyer, Cohen and Carlson 1918) application of heat to the skin (Bogendorfer and Snell, 1930 Bloomfield and Polland 1933 Bisgard and Nye, 1940, Henschel, Taylor and Keys, 1944) or of cold (Todd, 1930 Painter Todd and Kuenzel, 1939–40) depress gastric motility

The main factors which influence the emptying time of the stomach are

(*a*) the motility of the stomach itself, (*b*) the consistency of the gastric contents, (*c*) the osmotic pressure of the gastric contents, and (*d*) the quantity of material in the duodenum It should be remembered that the pressure in the antrum must exceed that in the duodenum for the stomach to empty Gastric evacuation is also influenced to some extent by the position of the body, emptying being more rapid when the subject is lying on his right side than when he is standing or recumbent on his left side (Best and Taylor, 1945)

THE REGULATION OF THE SECRETORY ACTIVITY OF THE DIGESTIVE PERIOD

The secretory activity of the gastric glands during the digestive period is regulated in the following manner Special stimuli are necessary for the elicitation of gastric secretion These may act either reflexly through the nervous system, giving rise to the first, or *nervous*, or *cephalic* phase of gastric secretion, or through the body fluids, giving rise to the second, or *chemical* phase of gastric secretion The composition of the gastric juice produced during the first phase differs in certain respects from that produced during the second phase (Babkin, 1944)

The cephalic phase

The cephalic phase (first studied by Pavlov) is provoked by stimuli such as the thought, the smell or the sight and taste of food These stimuli act in the presence of appetite through either conditioned or unconditioned reflexes It can also be produced by hypnotic suggestion and occurs in the absence of the cerebral cortex The vagi are the efferent nerves of the cephalic phase since section of these nerves, as well as the administration of atropine, abolishes this phase of secretion (Farrell 1928b) The gastric juice of the cephalic phase is highly acid and possesses considerable peptic activity, the amount of juice secreted is extremely variable The volume of secretion is affected by the appetite, the attitude of the subject, the type of food (agreeable or disagreeable) and the manner in which the food is prepared Carlson (1915a) confirmed the observations of Pavlov (1910) that the mere act of chewing indifferent substances and the stimulation of nerve endings in the mouth by substances other than those directly related to food cause no secretion of gastric juice The rate of secretion of gastric juice on mastication of palatable food is directly proportional to the palatability of the food (minimum rate 1 4 cc, maximum rate 10 8 cc, average 3 5 cc, per minute) On cessation of chewing the secretion rate diminishes rapidly so that in 15–20 minutes the gastric glands reach the level of the continuous gastric secretion, which varies from 2 to 50 cc per hour, the higher figure being exceptional

The acidity of the gastric juice depends on the rate of secretion—slow secretion allowing time for neutralization by the alkaline mucous membrane (Carlson Orr and Brinkman, 1914) Sham feeding of milk and sham drinking of water yield practically equal quantities of appetite gastric juice Meat

applied to the mouth of decerebrate dogs (sham feeding) excites gastric secretion (Zeliony, 1923)

Cowgill (1941) has pointed out that good cooking is the first stage in digestion and the only stage over which control can be voluntarily exercised

The chemical phase

Following the first or nervous phase of gastric secretion there is a second or *chemical* phase, which is subdivided into a *pyloric* and an *intestinal* phase

Pyloric phase

The pyloric phase of secretion can be stimulated by mechanical distension and secretagogues Feeding re-establishes peristalsis after fasting (24 hours) Drinking water on the part of the thirsty animal nearly always causes secretion of gastric juice (Auer, 1907) Physiological salt solution in the stomach does not stimulate the gastric glands (Edkins, 1906)

According to Pavlov (1910) distension is the only adequate type of mechanical stimulus known Absence of food means the absence of mechanical stimuli and cessation or diminution of the secretion of gastric juice and hence, a diminished acidity (Carlson, 1913) Mechanical distension of the stomach stimulates gastric secretion in man and dog in the latter with or without the vagi intact (Lim, Ivy and McCarthy, 1925b) Secretagogues may act *per se* or through the liberation of a gastric hormone The application of procaine to the gastric mucosa abolishes the secretory response to distension and to local application of secretagogues (Ivy, 1941)

Uvnas (1942) observed that if the blood supply to the pyloric region was obstructed the response of the gastric glands to vagal stimulation was reduced or nearly abolished indicating that the pyloric region might be instrumental not only in the chemical phase but also in the nervous phase of gastric secretion

Babkin (1938) suggested the following triple mechanism of the chemical phase of gastric secretions (1) there is first the formation of a hormone (gastrin) in the pyloric and perhaps also in the intestinal mucosa when certain substances present in the foodstuffs or formed from them during digestion react with the pyloric or intestinal mucous membrane (2) the direct secretagogue effect of some food substances, or some products of their digestion after they have been absorbed from the small intestine, (3) the direct effect produced on the vagal secretory centres by hypoglycaemia and by certain substances circulating in the blood

According to Ivy (1941) the secretion of the gastric phase in the dog is 100–250 cc in 5 hours (20–50 cc per hour with mechanical stimulation and 20–40 cc per hour with secretagogues) in man the gastric phase produces normally 225–350 cc in 5 hours

The intestinal phase

Secretagogues or chemical substances are the only type of stimuli which produce gastric secretion on application to the intestine Mild distension has

no effect Undue distension or irritation of the intestine at first inhibits gastric secretion, probably reflexly If injury to the mucosa is produced, stimulation may result from the absorption of secretagogues, possibly histamine, produced locally (Ivy, 1941) Secretagogues which act in the stomach also act in the intestine

The third phase is inhibited by atropine (Ivy, Lim and McCarthy, 1925) In the dog atropine in non-toxic doses can abolish the secretion of HCl produced by food in the Pavlov pouch, in the Heidenhain pouch and in transplanted subcutaneous gastric pouches without the myenteric plexus In man, atropine apparently does not abolish the chemical phase of secretion

THE EFFECT OF BILE

Beamer, Friedman, Thomas and Rehfuss (1944) found that following the introduction into the intestine, without special precautions, of substances such as ground meats or meat digests a secretion of gastric juice was *usually obtained On the other hand, when bile was prevented from* entering the stomach or accumulating in the intestine and only isotonic solutions were used, little or no gastric secretion was evoked In Pavlov pouch dogs in which products of protein digestion were instilled in the intestine while bile was allowed to regurgitate the test solution being prevented from doing so, secretion of gastric juice was observed to commence within half an hour after the first appearance of bile in the stomach The volume of gastric secretion varied roughly in proportion to the volume of bile which regurgitated and the duration of contact of the bile with the gastric mucosa When solutions of dog or ox bile were placed in the main stomach of the Pavlov pouch dog, the secretion of the pouch amounted on the average to 6 2 cc during the first hour following bile administration, while the volume for the control hour preceding bile administration was only 0 7 cc , thus confirming the early work of Sokolov (Pavlov 1910) Contrary to the results of Meyer, Ivy and McEnery (1924) they found that bile alone in the intestine did not stimulate gastric secretion With the normally innervated stomach or gastric pouch the introduction of potent gastric secretory stimulants into the intestine of fasting animals was followed by secretion only under special conditions (1) presence of bile in the stomach or intestine (2) intestinal irritation due to hypertonic solutions (3) a pre existing state of continuous gastric secretion, (4) possibly over-distension of the intestine They concluded that products of protein digestion alone do not elicit an intestinal phase of gastric secretion

THE INTESTINO INTESTINAL REFLEX

Savitch (1914) claimed that distension of the pyloric part of the stomach, in addition to stimulating the secretion of acid by the fundic glands (gastrin) also acted as a powerful stimulus of peptic secretion This was confirmed by Uvnäs (1948)

Pi Suñer and Puche (1925) found that the effect of intestinal distension on the intestine is the same as for the stomach, but the effect is less marked when

the distended segment is further from the stomach and nearer to the ileo-caecal valve

According to Pearcy and Van Liere (1926) distension of any portion of the gastro intestinal tract will produce inhibition of every portion of the tract, the part stimulated will respond by contraction After parallel experiments on the frog and the turtle Pearcy and Van Liere concluded that reflexes involving phylogenetically old mechanisms in the gut act locally, and that reflexes acting in the gut at a distance from the stimuli are phylogenetically recent and involve recent nervous structures

Hermann and Morin (1934) observed that distension of a segment of duodenum jejunum or ileum provokes proximally and distally to the distended segment a reflex inhibition showing a simultaneous arrest of contraction and marked fall of intestinal tonus The reflex is abolished by bilateral section of the splanchnics but persists after double vagotomy

Morin and Vial (1934a b c) showed that distension of the duodeneum or jejunum produced at the same time as an inhibition of the small intestine the cessation of spontaneous contractions of the stomach and a fall of gastric tonus, that the splanchnics contain the afferent and efferent segments of the reflex arc which is situated between the 6th dorsal and Ist lumbar nerve roots which coincide with the emergence of the spinal roots of the splanchnic nerves and that distension which exceeds a pressure of 3–4 cm of mercury is capable of producing the reflex if it is situated in any part of the intestinal tract distal to the pylorus

Lalich Meek and Herrin (1936) found that the intestino-gastric inhibitory reflex produced by stimulation of jejunal Thiry segments may be mediated by either sympathetic or vagal pathways They suggested that the difference between their results and those of Morin and Vial (1934) may possibly be due to the interference by the anaesthetic with the vagus and that failure to obtain the reflex after one set of pathways is destroyed does not preclude the possibility that the other set of nerves contains one limb of the reflex arc Chang and Hsu (1941–42) found that stimulation of a loop of intestine by pressure heat, mechanical injury or electrical stimulation of its afferent nerve causes an inhibition of the whole intestine

Youmans Karstens and Aumann (1942) found that only the sympathetic contains both afferent and efferent fibres According to Youmans (1944) the inhibition is accomplished primarily by means of a long reflex completed through segments D_7–L_2 of the spinal cord The thoraco-lumbar system provides both afferent and efferent pathways for the reflex. There is no evidence that the vagi contain either afferent or efferent pathways for the reflex which is not mediated through the decentralized pre aortic ganglia and plexuses The central connections for the reflex are mainly ipsi lateral and homosegmental Crowley (1942) observed that distension of an isolated loop of intestine with intact extrinsic nervous connections produced the same characteristic changes which were completely eliminated by section of the spinal cord at the level of the second thoracic vertebra or by section of the

Freund and Sheehan (1943) observed in the resected jejunal segments that the distension reflex was obtained after bilateral vagotomy and was abolished by removal of both sympathetic chains but not by bilateral splanchnicotomy or bilateral abdominal sympathectomy Section of the vagus after removal of the spinal cord from the cervical region downwards was without apparent effect (Kuntz and Saccomanno, 1944) Herrin and Meek (1945) observed that distension of a Thiry fistula in the first portion of the jejunum produced vomiting and anorexia, which was not abolished by vagotomy but was abolished by bilateral splanchnicotomy and excision of the lumbar sympathetic chain

The minimal pressure required to elicit the reflex is lowered—the effectiveness is greater—as the length of the jejunum distended is increased This may be explained on the basis of spatial summation in the central nervous system or in the autonomic ganglia involved (Peterson and Youmans, 1945)

THE INTERRELATION OF THE SECRETORY AND MOTOR FUNCTIONS

According to Edelman (1906) the movements of the stomach are related to the secretion of gastric juice Neutralization or dilution of the gastric juice results in the cessation of the movements which are restored only when the contents become again strongly acid Hedblom and Cannon (1909) observed that feeding of acid food was attended by a specially deep and rapid peristaltic wave According to Best and Cohnheim (1910) hyperacidity provokes hypermotility

Cannon (1911) observed that the two general factors of digestion, the chemical and mechanical which work towards the absorption of food, are intimately interrelated

The striking parallelism of response, under conditions of rest and muscular activity was reported by Hellebrandt and Dimmitt (1934), Hellebrandt and Tepper (1934), Wolf and Wolff (1943), Babkin (1944)

Hellebrandt (1935) concluded from her observations that recurrent hunger cycles of the human fasting stomach are associated with fluctuations in the acidity of the gastric contents and that these two phases of gastric function augment and subside in unison

The motility of stomachs in infancy increases or diminishes as the gastric acidity rises or falls (Davidsohn 1921)

Grossman (1950) considered that no final statement can be made as to whether or not there are separate physiological hormones for motor and secretory inhibition He argued that the motor inhibitor in intestinal extracts is not the physiological motor inhibitory hormone The secretory depressant in intestinal extracts may or may not be the physiological hormone if it is then the physiological hormones for motor and secretory inhibition are separable

In conclusion it may be recalled that stimulation of the vagi produces an increase in both the secretion and motility of the stomach and stimulation of

the splanchnics produces inhibition of both secretion and motility Section of these nerves produces simultaneously the opposite effect in both reactions The effect of sensory stimulation (sciatic nerve) as observed by the dilation of the pupils, produces inhibition of gastric peristalsis and inhibition of gastric secretion Electrical stimulation of the serosa of the secreting stomach produces an augmented secretion and contraction of the muscle fibres

It should be remembered, particularly from the point of view of its clinical application, that the functions of secretion and motility cannot be dissociated, that the factors which stimulate the one also stimulate the other, both responding simultaneously and in an identical manner to a given stimulus, and that the reverse process is equally true in as much as the pathological conditions which inhibit the one also inhibit the other function

CHAPTER 4

THE LAW OF ISOPERISTALSIS AND ITS COROLLARIES

THE LAW OF ISOPERISTALSIS

The behaviour of the peristaltic wave

It has been shown that the peristaltic wave forms the most important element in the transmission of the intestinal contents It may be initiated by nervous, physical and chemical stimuli The act of deglutition and the presence of food in the stomach provide the necessary stimuli

The regulation of the motor function of the gastro-intestinal tract appears to be composed of three elements (1) the local reaction of the smooth muscle, (2) the control of short distances by the connecting fibres of the intrinsic nervous system through the polarity of short strips of nerve fibres, (3) the control of long distances by the extrinsic nervous system

In their action on the gastro intestinal tract, the sympathetic and parasympathetic nerves do not display the antagonism which characterizes their action on other organs They are mixed nerves with a motor preponderance in the vagus and an inhibitory preponderance in the sympathetic

The grading of the strength of contraction is largely due to variations in the number and frequency of impulses discharged during each contraction, whether the nature of their response to visceral nerve fibres is all-or-none in character or graded (not all or none)

If one accepts the summation of responses or the hypothesis of quantum amounts of chemical mediators liberated in response to quantum nervous impulses the final result will produce a gradient effect which corresponds to the gradient theory of Alvarez and which may be interpreted as an adaptation to function The greatest number of responses will occur in the stomach which receives the greatest number of impulses the wave will be strongest at its origin, become weaker and gradually fade out its energy being absorbed as it travels down the gut If, however the wave is arrested either by an organic or functional obstruction before it is absorbed, it will be folded back on itself and its direction reversed This may happen but only to a slight extent in the terminal ileum when the waves butt against the caecum, but there is no evidence that normally reversed peristalsis occurs proximally to the ileo-caecal junction

It is self-evident that the factors which control the normal motor function of the gastro-intestinal tract whether myogenic or neurogenic, are only

concerned with the propulsion of the intestinal contents, there appears to be no physiological mechanism which actively reverses the direction of its forward movement The muscle fibres have their own local reactions which are dependent on a nervous system for the coordination of their individual functions The joint action of these two elements directs the orderly advance of the wave and while many local chemical processes take place it maintains a segmental equilibrium as part of a general equilibrium of the gut The term isoperistalsis has been suggested to describe this function in order to emphasize the general state of stability which persists at the same time as the succeeding waves move down the intestinal canal The peristaltic wave has a quantum value it submits to the laws of the ondulatory theory of elastic bodies that is it has amplitude, length (frequency) and speed of propagation (velocity) Frequency and velocity of the wave are the same before and after reflection but amplitude diminishes through absorption of part of its energy

The behaviour of the peristaltic wave which imposes the forward propul *sion of the intestinal contents, may be expressed as a law—the law of iso-*peristalsis—which postulates that the normal peristaltic wave invariably moves in an oral aboral direction and that when this forward direction is reversed it must be considered as a pathological deviation from the normal.

From the law of iso-peristalsis may be deduced the corollary of the function of the alimentary sphincters The alimentary sphincters act in two ways (1) *passively* as anatomically undifferentiated structures in the foreward transmission of the peristaltic wave, and (2) *actively* as functionally specia lized structures in the prevention of reflux of the intestinal contents at critical junctions (Spira, 1954)

THE GASTRO ILEAC GASTRO COLIC AND ILEO GASTRIC REFLEXES

The investigation of the gastro-ileac, gastro-colic and ileo-gastric reflexes throws further light on the motor function of the gastro-intestinal tract

Gastro-ileac reflex

The observation that the taking of food is followed by increased activity of the lower part of the ileum was referred to by MacEwen (1904) and confirmed on the human subject by Holzknecht (1909) Barclay (1912) Hurst (1913b) Hurst and Newton (1913), Case (1914c) and Short (1919)

Hinrichsen and Ivy (1931) believed that the gastro-ileal reflex (Hurst, 1913) or the duodeno-ileal reflex (Ivy and McIlvain 1923 Welch and Plant 1926 and Pearcy and Van Liere, 1926) is a true reflex They suggested that the duodeno-ileal reflex is a more correct term because the changes in the ileocaecal sphincter are more readily brought about by distension of the duodenum than distension of the stomach Douglas and Mann (1939) made observations on exteriorized loops in normal animals vagotomized animals animals with gastric fistulae animals in which the food residues were short-circuited past the loop and finally in animals with isolated loops A

regular cycle of activity was noted in the normal animal, a rapid motor response to feeding, followed by prolonged activity which gradually diminished until, after forty-eight hours of fasting, the activity was extremely feeble The motor response was noted as constant after feeding by gastric fistula as in the normal animal and after double thoracic vagotomy as before Complete isolation of the loop resulted in absence of the motor response to feeding They concluded that the degree and type of activity in the lower part of the ileum of the dog is intimately connected with the ingestion of food, that the so called gastro-ileac reflex is not merely a feeding reflex, that it depends for its mediation on the continuity of the intestine, and that the vagus nerves, which are generally believed to be the motor nerves of the small intestine, play little part in the mediation

Watkins and Mann (1949) observed in interchanged transplanted segments of jejunum and ileum that the rate of rhythmic contractions remained unchanged but the motor response to feeding depended on the relative position of the loop in relation to the remainder of the intestinal tract The more oral the loop, the quicker does the motor response occur after feeding

Alvarez (1948) agreed with Sokolov s (1940) view that the gastro ileac reflex is part of the wave which runs down the small bowel rapidly as soon as good-tasting food is put into the mouth

The gastro-colic reflex

The gastro-colic reflex appears to be an extension of the gastro-ileac reflex

Welch and Plant (1926) did not observe an effect upon the colonic activity when dogs received food through a gastric fistula, they rejected Hurst s (1913) view that the gastro colic reflex is dependent on the distension of the stomach and they contended that colonic activity is an appetite reflex similar to the appetite reflex in gastric secretion They also suggested the term "feeding reflex ' as a substitute for "gastro colic reflex" because they did not observe an increase in colon motility when food was introduced through a gastrostomy but an increase was observed when food was swallowed Monroe and Emery (1929) believed that the increase of activity of the colon after food could be explained on the gradient theory and was not a true gastro-colic reflex

Galapeaux and Templeton (1937) rejected this suggestion because they observed an augmentation which began shortly after the stomach was filled and increased progressively Douglas and Mann (1940) observed that the motor response occurred more rapidly after feeding by a duodenal fistula than by mouth and that the proximal part of the colon exhibited greater activity than the distal part After feeding, the distal colonic loop showed a constant motor response from 2 to 7 minutes after a meal In animals in which they exteriorized loops of small intestine at various levels they observed that the jejunal response occurred more rapidly than the ileac response and that in animals with two exteriorized loops the response appeared in the upper loop before passing on to the lower They concluded that following the ingestion of food a wave of activity travelling at the rate of about 1 cm per second passes down the length of the small intestine, the gastro colic reflex

does not appear to be part of this excitatory process and they questioned the reflex nature of the reaction Douglas (1941) observed a similar time relation of the reaction and he suggested that the function of the response is probably excretory The gastro-colic reflex is often followed by defaecation and it is probable that the gastro-ileac reflex represents defaecation of the small bowel into the colon Douglas (1949) observed in the duodenum a motor response to feeding similar to that observed at other levels of the small intestine and colon It provided further evidence that a wave of activity passes down the whole length of the bowel when food is first taken after a fast The time of appearance of the response in the duodenum is very similar to that of its appearance in the jejunum

Kinsella (1948) pointed out that "these gastro-ileac and gastro-colic reflexes are variable more marked on some days than on others, better developed in some people than in others, more marked after a large meal than after a small one The time at which the food reaches the caecum depends not only on the bulk but also on the composition and consistency of the meal

Bingham Ingelfinger and Smithwick (1951a) found in two patients that diarrhoea developed after sympathectomy and vagectomy and that therefore the gastro-colic reflex apparently persisted even when the alimentary tract is extrinsically denervated between the gastric cardia and the sigmoid

Thomas (1951) inserted two balloons 5 cm apart through a colonic fistula in a dog's duodenum so as to lie about 20 cm below the pylorus He observed that if 2 cc of N/10 HCl, 2 per cent soap solution or bile are injected between the balloons there follows an increase in tone and in amplitude of rhythmic contractions over the upper balloon and the opposite effect over the lower balloon If the injection is made above the upper balloon there is inhibition over both the balloons

The ileo-gastric reflex

Cannon (1909) stated that production of a weak tonus ring at the caecum (produced by a pinch or by Ba Cl_2) causes peristaltic waves to pass over the colon If the tonus ring is made at the terminus of the peristaltic waves anti peristaltic waves occur and sweep away the peristaltic waves If the tonus ring is made midway in the proximal colon the waves pass in either direction from the ring The tonus ring is therefore, the source of the waves Cole (1913) thought that the distended terminal ileum produced the reflex Barclay (1915) held a similar view

According to White (1918) delay in emptying the stomach is the exception and not the rule in lesions of the lower part of the intestine According to Alvarez (1940) there is some evidence of an ileo-gastric reflex that is if because of inflammation in the caecum or appendix the progress of material in the terminal segment of ileum is delayed or stopped there will be a slowing of progression in the duodenum Galapeaux and Templeton (1937) found that distension of the stomach with a balloon is as effective in eliciting defaecation in untrained animals as filling the stomach with a yeast and but termilk mixture Braithwaite (1942) described the ileo-gastric syndrome

with two types of stimuli which are responsible for its production (1) those arising in the gastric area producing phenomena in the ileo-caecal region, that is, the gastro ileac reflex, a normal non pathological sequence, and a true nerve reflex, (2) those arising in the ileo caecal region giving rise to symptoms and signs in the gastric area and probably of pathological origin This is the ileo-gastric syndrome proper, initiated by three conditions (*a*) chronic appen dicitis, (*b*) simple chronic ileo-caecal adenitis, and (*c*) chronic tuberculous adenitis Pylorospasm is present in a large percentage of these conditions together with delayed gastro-ileac reflex plus stasis and spasm of the ileo-caecal valve He suggested two theories as the possible cause of the syndrome (1) the lymphatic theory—infected lymph getting to the stomach, gall bladder and liver, (2) the nervous theory—impulses transmitted through the superior sympathetic plexus—producing epigastric pain, increased peristalsis and pylorospasm It may, however, be suggested that there is a third possibility, namely, that the syndrome is produced by retroperistalsis which is the effective factor of the ileo-gastric reflex

It may be stated, in conclusion, that the evidence supports the view that the so called gastro-ileac, gastro colic and ileo gastric reflexes do not exist but are phenomena which may be explained as simple applications of the law of isoperistalsis The gastro ileac and gastro colic reflexes become manifest with the arrival of the peristaltic waves at their respective locations, they appear at time intervals corresponding to the distance which they traverse, the ileo gastric reflex manifests its presence after the peristaltic waves have been obstructed and are reflected before they are absorbed when they appear proximally as antiperistaltic waves

RETROPERISTALSIS

It may be accepted as a general rule that the normal peristaltic wave invariably assumes a forward direction and that under ordinary conditions a reversal of the wave does not take place There is much evidence in support of this view (Elliott and Barclay Smith 1904) Schneller (1925) has pointed out that in accordance with the law of the intestine of Bayliss and Starling (1899) the forward movement in the gut is promoted while retroperistaltic movements will be inhibited There are however, circumstances which produce a reversal of the normal direction of the peristaltic wave

The reversal of the normal wave may be produced by several agents, it may appear as a secondary effect which follows the arrest of the normal peristaltic wave by a mechanical obstruction, which reflects the wave before it is absorbed Normally this phenomenon may be observed at the ileo-caecal junction where the differentiation of structure forms a natural obstacle to the progress of the peristaltic wave and returns it for a short distance into the ileum where it fades out It is too small to be significant gives rise to no symptoms and may, therefore, be ignored But when some obstruction in the gut is sufficient to interfere with the normal propulsion of the gastro-intestinal contents and gives rise to symptoms, then the reversal of the wave must be

considered as a pathological manifestation On the other hand the reversal of the wave which is brought about by some specific substances in the contents of the gut may be considered a biological phenomenon but may acquire secondarily the attributes of a pathological manifestation

The retroperistalsis associated with the general pathological conditions which produce nausea and vomiting and which include causes of central, reflex and toxaemic origin will not be taken into consideration as they are outside the scope of this thesis, the argument here presented will be limited to the phenomenon of the reversal of direction of the wave which occurs with the functional and organic disorders of the alimentary tract itself and with the organs which are directly associated with it

Obstructive factor

Experimental observations

It is self-evident that when a complete obstruction appears in the way of the forward progression of the intestinal contents it will be arrested and made to return from whence it came Hedblom and Cannon (1909) found that in cats they could slow the progress of food through the stomach and small intestine if they irritated the caecum sufficiently with croton oil Alvarez and Hosoi (1921b) who produced considerable inflammation in the tissues about the ileo-caecal sphincter of rabbits by injecting a few drops of turpentine into the sacculus rotundum observed that the animals suffered from diarrhoea and that the ileum was emptied orad Reverse waves in the pars pylorica of the stomach of rabbits suffering from mild dynamic obstruction (with no organic cause) of the small intestine were observed by Alvarez (1927) He considered that inflammatory lesions in the ileo-caecal region such as appendicitis may produce all grades of back pressure up to vomiting of large amounts of fluids Smith and Miller (1929) introduced an irritant croton oil into the proximal colon and air was introduced to cause moderate distension During the height of the increased activity reverse waves were often noted Similar effects were produced by irritation of the appendix and the gall bladder The reflex stimulation in the three cases was abolished by atropine Templeton and Lawson (1931) were unable to detect any contractions which they could classify definitely as antiperistaltic Child (1933) showed on Ctenophores that the longer one keeps stimulating the tissues corresponding to the lower end of the gradient the easier it is to produce reverse waves Auer and Krueger (1947) observed in an isolated segment of the descending colon in rabbits that a wave of inhibition precedes a wave of contraction They produced antiperistalsis by temporarily blocking a peristaltic wave the speed of the former being 1 to 4 of the speed of the latter Removal of the influences of the central nervous system abolished antiperistalsis

Clinical observations

Treves (1902) has noted that in acute intussusception violent symptoms of obstruction may occur in cases in which at operation little narrowing was found in the lumen of the bowel Roith (1912–13) believed that gangrene of

with two types of stimuli which are responsible for its production (1) those arising in the gastric area producing phenomena in the ileo-caecal region, that is, the gastro ileac reflex, a normal non pathological sequence, and a true nerve reflex, (2) those arising in the ileo caecal region giving rise to symptoms and signs in the gastric area and probably of pathological origin This is the ileo-gastric syndrome proper, initiated by three conditions (*a*) chronic appendicitis, (*b*) simple chronic ileo caecal adenitis, and (*c*) chronic tuberculous adenitis Pylorospasm is present in a large percentage of these conditions together with delayed gastro ileac reflex plus stasis and spasm of the ileo-caecal valve He suggested two theories as the possible cause of the syndrome (1) the lymphatic theory—infected lymph getting to the stomach, gall bladder and liver, (2) the nervous theory—impulses transmitted through the superior sympathetic plexus—producing epigastric pain, increased peristalsis and pylorospasm It may, however, be suggested that there is a third possibility, namely, that the syndrome is produced by retroperistalsis which is the effective factor of the ileo gastric reflex

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explains the presence of bile in the stomach after the administration of fatty foods as an attempt at intestinal digestion of fat in the stomach He emphasized that carbohydrates are never accompanied by regurgitation of bile during the digestive period Crider and Thomas (1937) observed that bile was found in the gastric contents regularly after olive oil had been given and that when Wesson oil was administered to the animal it produced vomiting They found that there was a greater delay in emptying when the *pylorus was kept open as compared to the control experiments* and it appeared to them that this was due to more frequent and extensive regurgitation from the duodenum Frazer (1940) pointed out that a surplus of neutral fat in the food results in delayed emptying of the stomach, and great excesses may cause vomiting, so that under normal circumstances it is impossible for more than carefully regulated quantities of fat to pass into the small intestine at one time

The effect of excessive acid was studied by Schmidt and Fogelson (1937) who observed vomiting and regurgitation of bile when they administered 0 50 per cent instead of 0 36 per cent hydrochloric acid to their oesophagotomized dogs Warkentin (1941) found that the introduction of acid into the intact upper jejunum will regularly induce enterogastric regurgitation after bilateral section of the splanchnics and vagi and excision of the coeliac ganglia This shows that such regurgitation may be mediated solely by the intrinsic enteric nerves

Retroperistalsis in the upper duodenum

Carnot (1913) and Carnot and Glénard (1913) observed in the isolated stomach and duodenum of cats only rare antiperistaltic waves in the corpus in the antrum there may be reverse waves if the pressure in the duodenal bulb is greater than that of the antrum In the duodenum regular antiperistaltic waves occur, but the duodenal bulb itself does not participate in these contractions

Ganter (1921) *in his studies on the movements of the duodenum did not* mention the occurrence of antiperistaltic waves nor did Barsony (1921) in his radiological studies Henderson (1923) stated that a true reverse peristalsis has never been observed According to Borcesco Béclère and Porcher (1927) antiperistaltic waves occur normally in the second portion of the duodenum but very rarely in the bulb A similar observation was made roentgenologically by Bolton and Salmon (1927) The pathological antiperistaltic movements occur invariably (according to Duval Roux and Béclère 1925) when the organ is dilated the dilatation being produced (1) by spasm from a proximal lesion or by reflex (appendix gall bladder), and (2) by compression (stenosis)

According to De Beule (1931) three pathological groups give rise to retroperistalsis (1) a mechanical *obstacle* (2) *duodenal paralysis* and (3) disequilibrium of innervation (through inflammatory processes gastro pyloro-duodenitis) Buckstein (1933) has occasionally seen reverse duodenal peristalsis with typical to and fro writhing movements which he thought were

the caecum in obstructive tumours of the sigmoid flexure is the effect of regurgitation resulting from antiperistalsis

Moynihan (1923) has pointed out that symptoms of duodenal ulcer may be produced in cases of chronic appendicitis especially where tuberculous glands are present in the ileo colic angle, in cases of obstruction of the duodenum in its third part by the superior mesenteric artery, by the ileo colic artery, or by tuberculous glands adherent to the duodenum, on either side of the superior mesenteric artery, in cases of chronic nicotine poisoning, and, in some cases of cholecystitis with or without stones In MacLean's (1932) study of 300 cases of chronic appendicitis, delay in the filling of the caecum was observed in about 50 per cent of the cases Alvarez (1940) pointed out that the commonest lesion at the lowest end of the small intestine is appendicitis which can produce all grades of intestinal back pressure, from a barely demonstrable ileac stasis to the vomiting of large amounts of intestinal fluid

It may therefore be deduced, that any obstruction, either functional or organic, which impedes or reverses the progress of the wave must produce delayed gastric emptying, an observation which has much clinical importance

The food factor

The second factor which is concerned with the regurgitation of the intestinal juices into the stomach is related to the gastric contents and more specifically to the presence of fat, no other foodstuff has a similar effect In addition to the inhibitory effect which fat has on the motor and secretory function of the stomach, it has been shown that the presence of fat in the upper duodenum is responsible for the reversal of the normal direction of the peristaltic wave Boldyreff (1904) stated that there are three definite conditions under which the intestinal juices enter the stomach in the experimental animal (1) when the stomach is empty after prolonged starvation, (2) by feeding with different types of fatty foods, (3) when there is an excess of acid present in the stomach

Cathcart (1911b) observed the regurgitation of bile after the administration of oil, oily or fatty foods and also after irritation of the pylorus Boldyreff (1915) gave experimental evidence that only fats give rise to regular duodenal regurgitation, definite observations having been made that this massive regurgitation consists of both bile and pancreatic secretion Grey (1917) explained the duodenal regurgitation after fat which is only slightly affected by the gastric juice as demonstrating how the duodenum may aid the stomach in its struggle with an unusual burden Lockwood and Chamberlain (1923a) observed biliary regurgitation in 10 out of 13 cases to whom they administered one ounce of olive oil before an Ewald test meal Ryle (1931) has pointed out that the ingestion of greasy or fatty dishes of paraffin or of castor oil, or the smell of frying provoke nausea, which is absent in those painful gastric disturbances like duodenal ulcer in which tonic and peristaltic activity are exaggerated (The explanation of this phenomenon will be found in the chapter which deals with the Syndrome of Hyperfunction) Rehfuss (1929)

has observed on the screen a drop of 3 inches in the lower border of the stomach just before fainting occurred and also when the patient was given nauseous substances to smell Keeton (1925) suggested that nausea results from a motor dysfunction of the duodenum most probably from a pathological antiperistalsis

Distension of the duodenum as a cause of nausea was observed by Ivy and Vloedman (1925) Wheelon (1926), Dragstedt and Palmer (1932) Ingelfinger and Moss (1942), Gruber (1944), Wolf (1946) Pennington Haney and Youmans (1946) produced nausea when they distended segments of the jejunum with pressures of 80–90 mm Hg

Wolf and Wolff (1943) found that the application of mustard to the stomach did not produce nausea but that nausea was produced when the mustard reached the duodenum and bile regurgitated into the stomach Wolf (1943) observed that nausea is usually associated with cessation of spontaneous gastric contractions and a decrease in the tone of the stomach

Gregory (1947) observed that the disappearance of nausea and vomiting following denervation of the mesenteric vascular pedicle to the Thiry Vella loop indicated that the changes are of central reflex origin

Vomiting

The relation of vomiting to nausea is shown by the fact that nausea usually precedes vomiting Cannon (1911c) saw only once during emesis an antiperistaltic constriction start at the pylorus and run back over the antrum completely obliterating the cavity but stopping at the incisura angularis The stomach plays a relatively passive role in vomiting

According to Luckhardt Phillips and Carlson (1919–20) vomiting is more easily induced by irritating the duodenal mucosa than by irritation of the gastric mucosa Wheelon (1921) found, experimentally that vomiting can be readily induced by rapid or gradual overdistension of the stomach or duodenum this is particularly well illustrated in the vomiting of infants According to Hatcher and Weiss (1923) the vomiting centre is embraced within the sensory nuclei of the vagi which are essential for vomiting however induced in the higher mammals Vomiting is possible after vagotomy because the sympathetic makes functional communication with the vomiting centre They stated that when a nauseant is absorbed the pylorus closes and remains closed during the continuance of the nausea According to Hatcher (1924) the afferent paths for emetic impulses from the stomach are (*a*) the sympathetic trunk the stellate ganglion and cord and (*b*) the vagus trunk Kratinoff and Sack (1927) also held that both the vagi and the sympathetics are the afferent paths in emesis They described a prodromal state in which the intestine contracts actively before the stomach moves and before the abdominal muscles and the diaphragm come into action, the contractions being rhythmic segmentations and not retroperistaltic waves Complete denervation abolishes vomiting

McDowall (1934) pointed out that vomiting is preceded by a profuse secretion of saliva due to reflex stimulation of the salivary glands The saliva

probably a pure physiological phenomenon, but he considered it abnormal when there was also a definite disturbance of motor function and abnormal delay of the emptying of the duodenum Brodin and Tedesco (1934) believed that the antiperistaltic waves observed in the second part of the duodenum were produced by slight compression of the duodenum by an inflamed appendix or by the right colon According to Barclay (1936) retroperistalsis in the stomach occurs sometimes in association with fairly extensive lesions involving the last inch of the lesser curvature He could stop the reverse peristalsis and re start the rhythm in the normal direction

According to Quigley and Meschan (1937) active reverse peristaltic movements do not occur except when nausea and vomiting supervene Mecray (1941) produced emesis in dogs and cats by injecting emesis containing small intestine contents (colloidal thorium dioxide—Thorotrast) into the serosa of the stomach and duodenum, although the vomit consisted of small intestine contents antiperistalsis was not observed Douglas (1949) could not find reliable evidence in the literature that under normal conditions antiperistalsis takes place in the duodenum nor could he observe it in his own experiments

Duodenal stasis may give rise to retroperistaltic waves and according to Debray and Pergola (1951) may be produced by intrinsic causes (ulcers, tumours, foreign bodies, polypi, angiomata) and by extrinsic causes (adhesions juxtaduodenal tumours compression by the mesenteric vessels ptosis, hepatobiliary, colonic and appendicular inflammations, megacolon)

According to Giraud and Naudin (1951) duodenal antiperistaltic waves are very marked in duodenal dyskinesias with dilatation of the second part of the duodenum in association with ulceration of the duodenal bulb

Retroperistalsis in relation to nausea and vomiting

Nausea (or the feeling of sickness) and vomiting will be dealt with together because they are so commonly associated that they are usually considered as parts of a single process, nausea being according to Hatcher and Weiss (1923) probably the more primitive function, vomiting being dependent upon the association of several independent reflexes

Nausea

It is a matter of common observation that animals (including man) do not eat during nausea When a systemically acting emetic nauseant is absorbed in sufficient amounts to induce nausea the pylorus closes and remains closed during the continuance of the nausea According to Hatcher and Weiss (1923) it serves as a protection against poisons (including injurious foods) by interrupting their ingestion and delaying absorption According to Rehfuss, Bergeim and Hawk (1914a) there is a flow of duodenal content back into the stomach at the end of a meal or during starvation, but it must be of a very mild character since it does not give rise to any symptoms Alvarez (1917) believed that nausea may be one of the symptoms elicited by intestinal antiperistalsis thus indicating its pathological significance Barclay (1932)

as it is in the adult, apparently on account of the incomplete development of the musculature (Bouslog 1942)

According to Wernstedt (1913), cross section of the pyloric sphincter as seen from the pyloric end appears as a triangular muscle and represents a contraction phenomenon This prism like "sphincter disappears with complete dilatation of the muscle In its place there appears a diaphragmatic type of valve with a muscle ring (Scheibenformung) which has the same thickness as the adjacent pyloric canal

Forsell (1913) described the pylorus as forming a wall of fibrous tissue which divides the stomach from the duodenum

According to Pernkopf (1924) a marked sulcus intermedius as well as the appearance of the pyloric canal and pyloric antrum which are visible in specimen fixed *in situ* are produced by contraction and are functionally conditioned

Horton (1928, 1931) described a complete break between the circular muscles of the pars pylorica and that of the duodenum and a discontinuity of the submucous lymphatics which explained the presence of a connective tissue septum between these organs the myenteric plexus was found to be continuous

According to Cole (1932b) the pyloric sphincter is the abrupt distal end of the fan shaped muscle which is located at or near the base of the valve The valve itself is composed of a double layer of mucosa muscularis mucosae and a core of submucosa

Bergmann compared the pyloric sphincter to the iris because the muscularis mucosae is radially disposed (Barclay, 1933)

According to Torgersen (1942) the pyloric sphincter is not an independent anatomical structure but belongs both to the pyloric antrum and to the first part of the duodenum

It should be noted that the pyloric vein which has been suggested by Moynihan as an important landmark in the separation of the pylorus from the duodenum may or may not be present but it is too variable in location to serve as an anatomical landmark (Lejars and Sabbey, Soulignoux Mat thieu Caille, Melchior quoted by Greggio, 1916)

Mayo s (1908) "anaemic spot visible on stretching is due according to Wilkie (1911a) to obliteration of the supraduodenal artery by stretch It may simulate a healed ulcer scar (Eusterman and Balfour, 1935)

THE MORPHOLOGICAL UNITY OF THE STOMACH AND FIRST PART OF THE DUODENUM

The view of an intimate relationship of the first part of the duodenum with the stomach was supported by Schwarz (1908), Mayo (1908b), Holz knecht (1910) Cole (1917, 1932), Reeves (1920) and Bergmann (1936)

The morphological unity of the first part of the duodenum is indicated embryologically The division of the archenteron into fore gut mid gut and hind gut represents three definite functional divisions and the division between the fore gut and the mid gut takes place at the entrance of the common bile duct into the primitive duct indicated by the evagination

mixed with air, accumulates to a considerable extent at the lower end of the stomach which is distended This may be explained (Cowgill, 1941) as an attempt to prevent vomiting by swallowing, thus inducing peristaltic waves in order to overcome reverse waves and reducing gastric acidity

THE FUNCTION OF THE ALIMENTARY SPHINCTERS

(*La fonction fait l'organe* — Claude Bernard)

The function of the alimentary sphincters which has been deduced as a corollary of the law of isoperistalsis, implies that failure to exercise their physiological function will produce pathological manifestations

There is much evidence to support the view that (1) failure of the cardiac sphincter may lead to inflammatory reactions in the oesophagus, (2) failure of the sphincter of Oddi to inflammatory reactions of the pancreas, (3) failure *of the pyloric sphincter to inflammatory reactions of the stomach (4) failure* of the ileo caecal sphincter ("La porte des Apothicaires") to inflammatory reactions of the terminal ileum, and (5) failure of Gerlach s valve to inflammatory reactions of the vermiform appendix

These items will not be referred to any further as they are not immediately relevant to the subject of this monograph Only the pyloric sphincter, which is involved in the pathogenesis of peptic ulcer, will be examined in some detail

References to the relevant sphincters are given in the Appendix

The pyloric sphincter

From the law of the intestine (Bayliss and Starling, 1899), the behaviour of the peristaltic wave and its corollary the function of the alimentary sphincters (Spira, 1954), it may be concluded—and it has been confirmed by observation—that retroperistalsis does not occur normally in the small intestine, since it has been postulated that reflux of bile into the stomach is the initial factor in the causation of chronic gastro duodenal ulcer (Spira, 1931) it necessarily infers the failure of the pyloric sphincter to exercise its physiological control It will, therefore, be necessary to examine the behaviour of the pyloric sphincter in some detail, in order to define the limitations of its function

Anatomical considerations

The pyloric sphincter constitutes the anatomical junction of the stomach to the duodenum

Cunningham (1906) described the extremity of the pyloric canal as protruding into the commencement of the duodenum When viewed from the duodenum it presents the appearance of a smooth rounded knob with a small puckered aperture, the pyloric opening in its centre and is surrounded by a shallow groove or fornix In the full time foetus this protrusion is more marked than in the adult

Schwalbe (1912) and Muller (1921) could not find a definitely demarcated pyloric valve in the foetus The pylorus in the normal infant is not distinct

ting the different portions of the gut where such exist but it is generally held that Brünner s glands are the direct continuation of the pyloric glands and while they are numerous near the pylorus they are hardly present beyond the entrance of the common bile duct and entirely absent in the lower duodenum According to Paschikis and Orator (1923) there is no fundamental difference between the cardiac, pyloric and Brünner s glands A similar view was held by Meulengracht (1935) Maximow and Bloom (1939) Florey, Wright and Jennings (1941) and Landboe Christensen (1944)

It has been shown that Brünner s glands resemble anatomically the pyloric glands it can also be shown that physiologically they respond to stimuli in a similar fashion Florey and Harding (1933, 1934) observed in cats with duodenal fistulae and in duodeni which had been transplanted subcutaneously and deprived of all nervous and vascular connections with the abdominal contents a similar response to feeding showing that some hormonal stimulus was involved Highly purified secretin injected intravenously caused typical secretion from the quiescent fistulae The hormonal response to feeding was confirmed experimentally by Blickenstaff and Gross man (1948) Meulengracht (1935) showed that extract of that part of the duodenum containing Brunner s glands was active in supplying the ' intrinsic factor of Castle for the treatment of pernicious anaemia He suggested that the cardiac part of the stomach the pyloric antrum and the first part of the duodenum which have certain histological similarities formed a "gland organ which secreted the factor

Wright, Jennings, Florey and Lium (1940) have shown that prolonged stimulation of the infracardiac vagi of decerebrate or decapitate cats regularly produces a considerable flow of mucoid juice from the first part of the duodenum which was shown to be identical with the mucous secretion of Brünner s glands Florey Wright and Jennings (1941) believed that Brünner's glands are responsible for a large part of the duodenal secretions and that mucin is their product

Physiological considerations

THE NERVOUS CONTROL

The extrinsic innervation of the pyloric sphincter is provided by the vagi and splanchnic nerves

The vagus nerve has been considered as entirely motor for the pyloric sphincter by Openchowski (1889) Langley (1898–99) Rossbach (1890) Katz and Winkler (1902) and Dixon (1902)

On the other hand the splanchnic was also considered to contain motor fibres by Schiff (1862) Contejean (1892), while the inhibitory action was shown by Oser (1892) Van Yzeren (1901) Katz and Winkler (1902) and Elliott (1905)

According to May (1904) the vagus contains both motor and inhibitory fibres while the splanchnic has no influence on the pylorus

The pyloric sphincter has a double nerve supply half of which is of bulbar origin coursing over the vagi and part of the spinal region distributed

which forms the liver (Keith, 1913) The blood supply of the three divisions of the gut is provided by three different arteries, the first part of the duodenum being supplied by a branch from the coeliac axis, while the remainder is supplied by branches of the superior and inferior mesenteric arteries respectively

According to Villemin (1922) there is always a constriction in the duodenum just above the ampulla of Vater (*retrécissement supra vatérien*) In the *embryo at the third month, only the upper part of the duodenum is well* developed The internal constituent parts are different for the upper and lower parts of the duodenum in respect of the mucosa, submucosa muscular layer and lymphoid tissue Morphologically, the upper part of the duodenum is distinguished in animals by its external and internal grey colouration, its dilated form which represents a small stomach in some species, its thicker muscular coat, its arteries supplied solely by the hepatic artery, in man it is distinguished by the absence of the valvulae conniventes, the absence of fixed lymphoid formations apart from the juxta pyloric lymphatic masses larger and more spaced villosities and fewer glands of Lieberkühn

Robertson and Hargis (1925) have pointed out that the first portion of the duodenum is free and movable and that the three other portions are retroperitoneal and fixed Smellie (reported by Cameron, 1925a) described a case of complete isolation of the stomach and first part of the duodenum which ended blindly (Bland Sutton s dictum "developmental abnormalities occur at the site of embryonic events') According to Keith (1910) rare, partial or complete constriction of the duodenum, of congenital or obscure origin, generally occurs at the part of the duodenum behind the opening of the bile ducts, which marks the junction of the fore gut with the mid gut

The folds of the gastric mucous membrane which are thicker than those of the intestinal mucous membrane enter the first part of the duodenum without altering their longitudinal direction an abrupt change of direction taking place as they reach the second part of the duodenum (Berg, 1926)

According to Saunders and Lindner (1940) the development of the first portion of the duodenum is closely associated with that of the stomach and shows an initial preponderance over the rest of the duodenum and in the formation of its essential curves In the embryo at 13 5 mm the first part is large and well developed and is almost twice the diameter of the succeeding *portion of the intestine*

BRUNNER'S GLANDS

According to Villemin *(1922) Brünner s glands* are placed astride the pylorus and resemble the pyloric glands to a very great extent He quotes Schlemmer (1870) Schwalbe (1872) Lenant (1879), Schiefferdecker (1884), Ellenberger (1887), Kuczinski (1890) Bochin and Davidoff (1895), Castellant (1898–99) Anile (1903) Deimler (1904) and Oppel (1910) who held similar views

Taylor (1927) stated that the transition from one type of epithelium to another is generally quite abrupt and coincides with the sphincters separa

authors from pH 4 8 to 7 97 (Okada and Arai, 1922), from pH 6 to 8 (McClure Montague and Campbell, 1924) from pH 5 90 to 8 23 (Hume Denis, Silverman and Irwin 1924), from pH 6 2 to 6 5 in dogs (Graham and Emery, 1928), from pH 6 6 to 7 3 (Miller and Abbott, 1934), from pH 6 21 to 7 06 for the ileum (Eastman and Miller, 1932), pH 3 0 near the pylorus more generally near 4 0 (Thomas 1940), pH 5 6 in the fasting state and 5 0 after an Ewald meal (Berk Rehfuss and Thomas 1942a)

McGee and Hastings (1942) found that normal jejunal juice was slightly acid (pH 6 5)

The effect of food on duodenal acidity — McClendon Myers Culligan and Geydesen (1919) found that the contents of the duodenum of infants and the small intestine in pups, dogs, cats, suckling rabbits (and adult rabbits on a sugar diet) were acid and the only place where alkalinity was found was the last part of the ileum in the herbivora on a diet deficient in soluble carbohydrates

McClure Montague and Campbell (1924) found that the pH of the duodenal contents varied according to the food, being acid after protein and alkaline after fat and carbohydrate The pH obtained while fasting or after the ingestion of tap water was always alkaline

No difference of reaction was observed by Hume, Denis, Silverman and Irwin (1924) Grayzel and Miller (1927) or by Thomas and Crider (1935–36) but according to Berk Rehfuss and Thomas (1942b) the acidity of the con tents of the duodenal bulb is largely determined by the type of food undergoing digestion and is related only in part to the degree of the gastric acidity

The effect of the chemical reaction of the stomach on gastric function — Hirsch (1893a b) and Serdjukow (1899) observed that alkali placed in the stomach left it with greater rapidity than acid Gastric motility was hastened with 0 25 per cent but lessened with 1 0 per cent hydrochloric acid in the stomach (Hedblom and Cannon 1909) These observations were confirmed by Marks (1928) Serby and Dooley (1930) Elman and Rowlette (1931)

Carnot and Chassevant (1905a b c) found that acid solutions in the stomach tend towards a chemical equilibrium of isotonicity Best and Cohnheim (1910a) also believed that the effect of acid in the stomach was not responsible for the pyloric reflex Pavlov (1910) found that spontaneous movements of the stomach cease when acid is poured into the stomach through a fistula

Retardation of gastric emptying by acid in the stomach was observed by Tabora (1911) Cowie and Lyon (1911) Lenk and Eisler (1913), Ladd (1914) Neilson and Lipzits (1915) Egan (1915, 1922) Morse (1916), Ortner (1917) McClure, Reynolds and Schwarz (1920) Baird Campbell and Hern (1924a b), Barsony Polgar and Szemzo (1924–25) Klein (1926c) Marks (1928) Stewart and Boldyreff (1932) Gianturco (1933b) Thomas Crider and Mogan (1934) Shay and Gershon Cohen (1934) Van Liere and Sleeth (1940), and by Roka and Lajtha (1950)

The effect of hydrochloric acid in the duodenum — Oppenheimer (1889) suggested that the opening of the pylorus was probably a function of the

through the splanchnics, but their origin and course does not determine their function Both carry motor and inhibitory impulses to the pyloric sphincter as well as the stomach, both nerves being mainly motor in function Inhibitory fibres are found in both nerves but more in the splanchnics than in the vagi (Thomas and Wheelon, 1922, Carlson and Litt, 1924) Thomas (1929) considered that the conception of the extrinsic nerves as consisting of some fibres that are constantly motor in function and others constantly inhibitory, as suggested by Carlson, Boyd and Pearcy (1922a) and Carlson and Litt (1924), is not adequate to explain the varied reaction that may be obtained when these nerves are stimulated The results with adrenaline are interpreted as indicative of a slight preponderance of inhibitory over motor components in the thoraco lumbar sympathetic innervation, governing the tonus of the pyloric sphincter in the dog and cat, and marked preponderance of motor over inhibitory components in the rabbit Afferent fibres (in the cat) are found in both the vagi and splanchnic nerves, the vagus nerve endings being more sensitive than the splanchnics (Irving and McSwiney, 1935) Quigley and Louckes (1951) found that complete vagotomy produced no significant change in the frequency of the sphincter contraction

THE CHEMICAL CONTROL

Hirsch (1893a, b), who quotes Pfungen who suggested that alkalis in the stomach open while acids close the pylorus, observed in dogs with duodenal fistulae that gastric reaction had no effect on pyloric opening and closure The higher the concentration of organic acids, the slower the gastric contents left the stomach Water flows out almost immediately

Cannon s law (1904) postulates the opening of the sphincter by the presence of acid on the gastric side and closing of the sphincter by the presence of acid on the duodenal side

Arguments in refutation of Cannon's theory

The arguments against Cannon s law will be considered under the following headings (*a*) the normal hydrogen ion concentration of the upper part of the duodenum (*b*) the effect of food on duodenal acidity, (*c*) the effect of the chemical reaction of the stomach on gastric function, and (d) the effect of hydrochloric acid in the duodenum

The normal hydrogen ion concentration of the upper duodenum — McClendon (1915) and McClendon, Myers, Culligan and Geydesen (1919) have shown that the infant s duodenum is more acid than the average acidity of the stomach Long and Fenger (1917) in electrometric determinations of the hydrogen ion concentration of the intestinal contents in man found that the *p*H was 2 27 five inches below the pylorus, four hours after a mixed meal They found the upper third of the intestine most strongly acid in hogs, lambs and calves McClendon, Bissel, Lowe and Meyer (1920) observed an acidity which varied from *p*H 4 1 to 6 5 in two healthy men who swallowed 36 inches of a gastric tube The hydrogen ion concentration of duodenal contents aspirated at the height of digestion ranged from *p*H 3 8 to *p*H 7 54 (Meyers and McClendon, 1920) The duodenal reaction was found to vary by different

tic juice necessary to produce the reduction in gastric acidity noted is far beyond the ability of any pancreas to secrete during the time allotted This observation was confirmed by Enderlen, Freudenberger and Redwitz (1923) and Kesavalu and Mann (1943)

Hicks and Visher (1915–16) considered that their observations are in accord with Starling s and Cannon s statement that 'an antiperistalsis is never observed in the small intestine ' Rehfuss and Hawk (1920) reasserted that the introduction of very high acidities (0 5 per cent HCl) in a human subject causes regurgitation of the alkaline intestinal secretion which they interpret as an autoregulatory mechanism Similar observations were made by Burget and Steinberg (1922) Moppert (1921) reported the "spontaneous reflux of bile in 72 per cent of cases which he examined by means of the Einhorn thread Jarno and Vandorfy (1921) found regurgitation in the human stomach after the introduction of weak acid solutions Baird, Campbell and Hern (1924a) observed that the early appearance of bile in the upper duodenum (40 seconds) makes it hardly possible that any chemical mechanism could be effective Ryle (1926) thought that reciprocal action as between the tonus of the pars pylorica and the duodenum plays a more important part in regulating (1) fluid outflow, and (2) gastric acidity and the opening and shutting of the pylorus proper

Bolton and Salmond (1927) thought that the acidity of the gastric content is quite a secondary consideration and that as long as the sphincter acts normally the amount of the gastric juices secreted is of little moment In the early stages it prevents regurgitation but relaxes as digestion proceeds independently of gastric peristalsis, promotes regurgitation and thus regulates the acidity of the gastric content

Yesko (1928) observed that after ligation and evulsion of the pancreatic ducts there is only a slight rise in gastric acidity McCann (1929a) showed in Mann Williamson dogs that when all the duodenal alkaline juices were shunted away from the pylorus into the distal portion of the ileum post operative fractional analysis did not show variations from the curves found before operation so far as they represented the chemistry of digestion or the control of acidity of the juice Whether part or all of the duodenal secretions are eliminated there is no tendency toward a condition of hyperacidity in the stomach Elman and Rowlette (1931) by dividing the pyloric sphincter produced a persistent lowering of the gastric acidity due to duodenal regurgitation but they also noted an increase in the gastric emptying time Shay Katz and Schloss (1932) rejected Cathcart s (1911b) statement that as a general rule, the stronger the acid introduced into the fundus of the stomach the earlier the regurgitation takes place In their opinion achlorhydria is frequently responsible for regurgitation on account of the poorly controlled pyloric mechanism which is the result rather than the cause of achlorhydria They explain the reduction of acidity after the introduction of strong acid in the stomach as one of absorption because changes of volume take place

Stewart and Boldyreff (1932) considered that duodenal regurgitation is

bowel rather than of the stomach, Moritz (1901) found that acid placed in the duodenum slowed the emptying time of the stomach, an observation confirmed by Tobler (1905) Best and Cohnheim (1910a) also believed that the effect of acid in the stomach was not responsible for the pyloric reflex but was an intestinal reflex independent of the stomach Pavlov (1910) found that spontaneous movements of the stomach cease when acid is poured into the stomach through a fistula but the movements are more effectively arrested by the action of acid in the duodenum

Reflex inhibition of gastric motility due to acid in the duodenum has been observed in the empty stomach by Sokolov (1904), Boldyreff (1904), Brunemeier and Carlson (1914) and, in the antrum separated from the rest of the stomach, by Kirschner and Mangold (1911) Barsony and Egan (1925) although they produced inhibition of the human stomach by placing acid in the duodenum, considered that the requisite stimuli were in excess of the normal Thomas and Mogan (1931) observed that HCl N/10 in the duodenum inhibits the contractions of the pars pylorica in both the full and empty stomach They found (Thomas, Crider and Mogan, 1934) that the acid in the duodenum does not cause more than a temporary contraction of the pyloric sphincter unles the stimulus is sufficient to cause vomiting

Frumin (1942) found that the introduction of 0 5 per cent solution of hydrochloric acid into the duodenum inhibited gastric contractions and doubled the evacuation time

Gershon Cohen (1947) dripped a hypertonic solution of sodium bicarbonate slowly into the duodenum and bathed the gastric side of the pylorus with 0 5 per cent hydrochloric acid Gastric emptying was completely prevented The pylorus remained closed and gastric peristalsis was in abeyance as long as the hypertonic alkaline solution was dripped into the duodenum

Bassi and Lorenzini (1951) found that peristalsis was inhibited by displacement of the duodenal *p*H to acid, and that the effect persisted as long as the *p*H remained below 6 8

Duodenal regurgitation in relation to the regulation of the gastric acidity (evidence in refutation of Boldyreff's theory) — Boldyreff (1904) advanced the theory of the regurgitation of pancreatic juice into the stomach as an automatic function which reduces the acidity of the gastric juice to its optimum concentration of 0 15–0 2 per cent According to his view, the acid passes into the duodenum and induces an abundant secretion, chiefly pancreatic juice, and if there is not sufficient pancreatic juice to achieve the required neutralization then bile and intestinal juices are also brought into play Boldyreff stated that bile and intestinal juice have a small degree of alkalinity and that under normal conditions they do not participate in the proce s of neutralization which is accomplished by the pancreatic juice

Spencer, Meyer Rehfuss and Hawk (1915–16) considered that their work in many ways confirmed Boldyreff s theory of ' the self regulation of the acidity of the stomach , because they found regurgitation in the normal human stomach Shay, Katz and Schloss (1932) rejected the evidence of Spencer Meyer, Rehfuss and Hawk (1915) because the amount of pancrea

pressure changes of the bulb are generally closely related to those in the antrum They are produced respectively by bulbar or antral contractions (Brody, Werle, Meschan and Quigley, 1940)

Tonus of pyloric sphincter —The tonus of the pyloric sphincter is low when the stomach is empty and increases during digestion (Thomas, 1931) when it remains practically constant (Quigley, Loukes and Brody, 1951) It appears to depend on a local excitatory (myenteric) reflex and a central inhibitory (enterogastric) reflex (Thomas, Crider and Mogan 1934)

The effect of duodenal stimulation — Pavlov (1910) stated that there are other conditions in the duodenum which have an effect on the sphincter similar to that of acid In the experiments of von Mering (1893, 1898) it was found that milk, a neutral fluid, when introduced into a duodenal fistula caused a reflex closure of the pylorus and retarded the emptying of the stomach (The results were due to the fat contained in the milk and egg yolk) However, filling long areas of intestine with fluid inhibits gastric emptying (Marbaix, 1898)

Cohnheim and Dreyfus (1908) found in the dog, that when little food was in the stomach, 10 cc of gastric contents injected through a fistula into the duodenum closed the pylorus for 10–15 minutes, but when the stomach was full, the same stimulus stopped the flow for only a minute or two

Distension of the duodenum by a balloon (Tobler, 1905, Carnot, 1908, Spurrell, 1935) by food, by tickling with a feather (Katsch, 1912) or tap water or saline solutions (Thomas and Mogan, 1931) will retard emptying of the stomach

McClure Reynolds and Schwartz (1920) found that pulling on the duo denal tube arrests gastric perisalsis

According to Carlson (1923) in animals not only acid but even alkaline stimulation of the duodenum can produce pyloric closure and he considers this to be the result of simple sensory stimulation

Mechanical irritation of the duodenal mucosa, through a duodenal fistula in dogs with extrinsic nerves to the stomach and intestine intact, elicits tonic contractions of the pyloric sphincter (Luckhardt Phillips and Carlson 1919) as well as following section of both vagi and splanchnic nerves (Thomas and Kuntz 1926) However the same reaction could not be elicited when conduction through the local neuromuscular mechanism was arrested by compression of the wall of the proximal portion of the duodenum between a ligature on the outside and a solid cylindrical body in the lumen (Thomas and Kuntz, 1926)

Thomas Crider and Mogan (1934) made the significant observation that the normal duodenal contents were found to act as adequate stimuli for the reflex mechanism causing inhibition of gastric peristalsis, draining the duodenum while the stomach was emptying regularly increased the force of peristaltic contractions

The role of the duodenum in gastric emptying —Hirsch (1892) and von Mering (1893) independently discovered that the passage of food from the stomach into the intestine is quantitatively regulated from the upper segment of the

the most important factor in the neutralization of gastric acidity MacLagan (1934), who attempted a statistical analysis of 389 fractional test meals with special reference to duodenal regurgitation, concluded that the results of his analysis give no support to the two theories which it was designed to test, namely (1) that in the normal individual duodenal regurgitation occurred towards the end of the test meal and is responsible for the fall in acidity which often takes place at that time and (2) that "hyperacidity" of the "climbing curve' is usually due to interference with pyloric relaxation either by organic or reflex causes and that this results in favour of duodenal regurgitation and undue retention of the products of digestion He supports MacLean's (1928) contention that duodenal regurgitation, when it occurs is an accident and in no way connected with the reduction of hydrochloric acid and the associated rise of neutral chloride which occurs during digestion

According to Bolton and Goodhart (1936) the pancreatic secretion induced by high waves of acidity is driven into the stomach by strong anti peristaltic waves due to irritation of the stomach which cannot tolerate an acidity in excess of 0 1–0 15 per cent HCl According to Ihre (1939) duodenal reflux is only exceptionally a factor in the acid reducing process which appears to be subject to a diffusion process Kesavalu and Mann (1943) showed on dogs with a pyloric fistula that the duodenal regurgitation into the stomach, as determined by the presence of visible bile, occurs infrequently in the fasting state as well as during digestion Bablin (1944) observed that toward the end of the secretory period there is a marked increase in the amount of non acid secretions entering the stomach Lambling and Gosset (1947) who studied *in vitro* the neutralization of the gastric juice, refute Boldyreff's theory because they found that an equal mixture of N/10 HCl and human pancreatic juice abolishes free acidity but leaves total acidity at 74 m Eq l

It may be stated, in conclusion, that the evidence tends to support the view that duodenal regurgitation is not a normal physiological phemenon Furthermore, McCann (1929c) showed that drainage of the whole volume of duodenal contents into the fundus of the stomach had little effect on gastric acidity Weiss, Graves and Gurriaran (1932) viewed the duodenal reflux as a 'réflexe de défense Maier and Grossman (1937) observed considerable digestive disturbances as a result of complete duodenal regurgitation Schmilinsky (1918) placed the afferent loop in the Billroth II type of gastric resection into the stomach in order to neutralize the gastric acidity with the duodenal secretions but the results of this operation, according to Lannin (1945), have proved to be disastrous

PHYSICAL CONTROL

Intra gastric pressure — The basal pressure of the pyloric antrum usually exceeds the basal pressure in the duodenal bulb and both rise moderately when food enters the stomach Subatmospheric pressure changes amounting to about 30 cm of water develop periodically in both regions The phasic

distal end of the thickened band of muscle which surrounds the pars pylorica and contracts exactly as the segments orad to it (Thomas and Wheelon 1922, McCann, 1929a, Thomas, Crider and Mogan, 1934, Meschan and Quigley 1938 Alvarez, 1948, Bassi and Lorenzini, 1951, Gibb, 1953)

The patency of the resting pylorus — The roentgenological observation (Holzknecht and Jonas, 1909), the suggestion (Spencer Meyer, Rehfuss and Hawk 1915–16, Rehfuss and Hawk, 1921 Baird, Campbell and Hern, 1921) and the deduction arrived at from theoretical considerations that the pylorus is patent at rest (Spira, 1931) has been confirmed by the balloon method (Meschan and Quigley 1938 Quigley, Werle and Brody 1940) and by gastroscopy (Alvarez, 1940 Gibb 1942, Quigley and Read, 1942, Roka and Lajtha 1950, Gibb 1953)

Exclusion of the pylorus —Surgical exclusion of the pylorus in experimental animals (von Mering 1897 Cannon and Blake, 1905, Shay and Gershon Cohen 1935 Crisler and Van Liere, 1936) and in the human (Tanaka 1935) or by cannulation (Crider and Thomas 1937) causes no significant difference in the time of gastric evacuation

The behaviour of the anastomotic stoma

Cannon and Blake (1905) pointed out that the gastric component of a gastro-intestinal stoma hypertrophies and acts as a valve, allowing exit from but preventing regurgitation into the stomach Truesdale (1915) showed that gastro-enterostomy produced atrophy of the pyloric ring Horwitz, Alvarez and Ascanio (1928) confirmed this observation

Meyer and Schmidt (1930) found that sphincter action may develop at any gastrointestinal anastomosis According to Beresov and Stern (1932) the Haberer modification of the Billroth I partial gastrectomy produces a functional closure which resembles that of the pyloric sphincter According to Tanaka (1935) the Billroth II anastomosis produces a spasm of the afferent loop 5–7 cm from the anastomosis

Schindler (1937b 1940) has repeatedly emphasized that rhythmic adaptation of the stoma with its controlling influence over jejunal reflux is the most *significant feature to be found in the postoperative stomach which is free of* gastritis

Vitkin (1940) thought that an effective stomal sphincter (which prevents gastric emptying) cannot be created by the surgeon at the site of anastomosis because it is impossible to establish artificially a reflex mechanism Schindler and Dailey (1941) concluded from their gastroscopic observations that the development of sphincteric activity is a general property of any portion of the antrum Although they could not say what mechanism initiates the sphincter action of artificial stomas they believed that it is not necessary to assume a nervous control as a requisite since the musculature of the distal portion of the stomach possesses the intrinsic capacity to produce rhythmical sphincter contractions at any stoma Brown and McHardy (1944) confirmed that a rhythmical stoma is usually present after gastrectomy Schindler (1947)

latter in such a way that a discharge of food from the stomach is temporarily restrained by a reflex from the duodenum whereby the pylorus is closed each time after a portion of the stomach contents has passed into the intestine

Cannon (1906) observed that the difference in the rate of discharge of different kinds of food from the stomach persists following section of both splanchnics and both vagus nerves Cole (1913) thought that the duodenal receptivity controls the evacuation of the cap through duodenal peristalsis rather than the evacuation of the stomach through a pyloric reflex Cole (1917) suggested that the duodenal pyloric sphincter reflex produced by the replete intestine does not affect the pyloric sphincter (as believed by Marbaix, 1898) but reacts on the contractions which withdraw the chyme from the reservoir cap, and that this process is similar to the one by which the duodenum is replenished from the stomach Wheelon and Thomas (1922) support the view that the degree of receptivity of the small intestine is as great a factor in the emptying of the cap as the motility of the stomach is in filling it They observed that the pyloric sphincter exhibits an active contraction when peristaltic activity occurs in the first part of the duodenum Cannon explained that the full stomach is essentially analogous to a bag full of water suspended in water and will, therefore, not empty by simple drainage due to gravity

When the chyme is aspirated from the proximal duodenum as rapidly as it enters from the stomach gastric emptying is increased several fold (Quigley, Meschan, Werle, Ligon, Read and Radzow, 1941)

Fat introduced either into the stomach or duodenum causes reflex closing of the pyloric sphincter (Lintwarev, 1903, Verzar and McDougall, 1936, Waugh, 1936)

The functional unity of the antrum, pylorus and duodenal cap — There is much evidence that the antrum, pylorus and duodenal bulb form a functional unit Schiff (1868) found that the pylorus did not open with each peristaltic wave, while according to Levan (1879) the sphincter contracts and dilates together with the pyloric antrum Moritz (1895) and Kirschner and Mangold (1911) observed in duodenal fistula dogs the same rhythmic contractions of the pars pylorica as for the stomach Cannon (1907–08) found roentgenologically in cats that the closure of the pylorus did not affect the movements of the antrum Cole (1917) showed radiologically that in man the period of opening of the pylorus and the passage of the fluid content into the duodenum was coincident with the tonus rhythm of the stomach The antrum, pylorus and duodenal bulb form a functional unit (Wheelon and Thomas 1920) which is established by the progression of the peristaltic wave and is demonstrated by the time relation in the contraction of the constituent parts Following a brief interval during which all three regions are simultaneously relaxed, a contraction occurs in the antrum which expels the antral contents into the relaxed bulb These observations have been confirmed by Cunha (1925) and Gianturco (1933) This co-ordinated relationship is not altered by vagotomy (Meschan and Quigley 1938) The pyloric ring behaves as the

distal end of the thickened band of muscle which surrounds the pars pylorica and contracts exactly as the segments orad to it (Thomas and Wheelon 1922, McCann, 1929a, Thomas, Crider and Mogan 1934, Meschan and Quigley, 1938 Alvarez 1948, Bassi and Lorenzini 1951, Gibb 1953)

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pointed out that when both stomal and pyloric contractions can be observed in one stomach, the former is more rapid than the latter Stomal rhythm is also independent of peristalsis in the adjacent jejunal segment

According to Boller (1947) the sphincter (pseudo pyloric) function of the anastomosis is conditioned by the peristaltic action of the small intestine, relaxation producing opening and contraction closure of the stoma This does not occur in the atonic stomach (Brauch, 1938)

Conclusions

It may now be stated, in conclusion, that the available evidence tends to indicate that the function of the pyloric sphincter is to prevent reflux of the intestinal juices into the stomach (Spira, 1931, Cole, 1932b, Crider and Thomas 1937, Torgersen, 1942, Gibb 1942) The pyloric sphincter behaves *passively*, by allowing the unimpeded forward movement of the peristaltic wave, and *actively*, when the necessity arises to hinder the reflux of the intestinal juices into the stomach in order to protect the structures which lie behind the sphincter It thus submits to, and further supports, the Law of Isoperistalsis Failure of the pylorus will give rise to hyperfunction of the stomach and pylorospasm (Cannon and Murphy, 1906, Hamburger and Friedman, 1914, Carlson and Ginsburg, 1915–16, Elsesser, 1915–16, Bergmann, 1918, Barber and Stewart, 1919–20, Thomas and Wheelon, 1922 Carlson and Litt, 1924, Hughson 1925, 1927a, Ivy, 1941, Quigley, 1943) and the persistence of its failure will allow the setting up of a chronic pathological condition in the mucous membrane of the stomach

PART II

PATHOLOGICAL CONSIDERATIONS

The peptic ulcer problem will be studied by examining the histological appearance of the lesions which represent the final phase in the evolution of the disease when the morbid process may be considered to have attained maximal activity Since the ' established stage of the lesion offers little possibility for analytical speculation it must be viewed in the light of clinical experience and interpreted in relation to the fluctuating process responsible for its evolution Recourse to an inductive method of reasoning will be necessary in order to link the morphology to the symptomatology The following plan will, therefore, be adopted (*a*) the gross and minute characteristics of the lesions will be described and their differences emphasized in order to provide the basis for a definition of the category to which they belong, (*b*) evidence will be brought forward to support the view that the acute and chronic ulcer represent two independent unrelated disease entities and that the gastric and duodenal lesions are fundamentally similar manifestations, (*c*) the significance of haemorrhage and perforation and the problem of malignant transformation will then be investigated

Pain and Experimental Ulcer will also be studied

PATHOLOGICAL ANATOMY OF PEPTIC ULCER

Ivy, Grossman and Bachrach (1950) define peptic ulcer as a benign, non specific ulcer located in those portions of the alimentary tract bathed by gastric juice There are two distinct types of ulcer, the acute and the chronic The pathological anatomy of the lesions will be described in order to define the characteristic features which establish their identity and their respective modes of origin

MORBID ANATOMY OF ACUTE AND CHRONIC ULCERS

The acute ulcer

Macroscopically the acute ulcer (the 'exulceratio simplex of Dieulafoy —the acute haemorrhagic erosion of Cruveilhier—the follicular ulcer) is usually described as being small in size round or oval in shape, sharply defined but multiple and widely and irregularly distributed It appears as a superficial necrotic lesion of the mucous membrane with raised and slightly reddened margins The floor is clean and smooth when the slough which is infiltrated with blood, is removed If the ulcer penetrates deeper it appears "punched-out with clean cut edges There is a narrow inflammatory border round the lesion but no thickening of the peritoneal surface The mucous membrane surrounding the ring of inflammatory reaction frequently shows no abnormality

Microscopically there is very little cellular reaction—a slight increase in the neutrophil leucocytes and lymphocytes Eosinophil cells are absent (Stewart 1929)

Haemorrhagic erosions are defined by Cruveilhier (1839) as lenticular spots of variable extent which are formed by a dense adherent clot of blood, the removal of which leaves a very superficial erosion He believed that the erosions did not begin in the tubules but more probably in the capillary bed of the mucosa Hayem (1911) considered that the simple erosion affects the mucous membrane only superficially and frequently does not penetrate beyond it although there is no reason if the morbid process is sufficiently virulent why it should not affect all the layers of the gastric wall and lead to perforation The primary lesion is formed by a focus of necrosis and becomes apparent only after removal of the scab the erosion may be either follicular or haemorrhagic containing masses of infiltration which burst in a manner similar to miliary abcesses The lesion is usually cone shaped surrounded

by a bed of dilated capillaries and lymphatic spaces, and there may be some vascular spasm causing the return of the blood flow to be impeded, thus giving rise to sub mucosal oedema with or without hyaline degeneration

Elliot (1913–14) described the pathology of the acute ulcer in the dog which followed 1–2 hours after the injection of tetrahydro β naphthylamine A state of psychic alarm and anger was produced, with consequent nervous exhaustion of adrenaline Externally the lesion could be recognized by purple coloured patches of congestion seen through the peritoneal coat

An irregular swollen patch of haemorrhage and erosion was surrounded by a wide margin of greyish colour without haemorrhage The cells of the overlying mucous membrane seemed normal The blood was soon absorbed as the circulation improved, the mucous membrane remained intact and ulcers never developed in the duodenum

According to Hauser (1926) erosions and acute ulcers are produced by haemorrhagic infarcts which are usually situated in the arterial bed and are caused by arterial disease (atherosclerosis in the aged), emboli (sepsis or excretion of toxins) or by arterial spasm of neurogenic origin which occurs mostly in young people The conception of the haemorrhagic erosion as an infarct limited to the mucosa has been supported by Rokitansky, Kundrath, Orth, E Kaufman, Ribbert and Schmaus Herz Weiner in their textbooks Willigk (1854) is reported as insisting that erosion and ulcer must have different bases of origin

Redwitz and Fuss (1928) found that the histological examination of acute and subacute ulcers shows a necrotic defect and a hyperaemic zone, but only a slight cell infiltration, in the wall and surrounding areas, so that young lesions can easily be mistaken for artefacts Hamperl (1932-33) distinguished between two types of haemorrhagic erosions (*a*) those which originate in the deep substance of the mucosa, and (*b*) those which occur on the surface of the mucous membrane and are affected by hydrochloric acid Penner and Bernheim (1939) showed that the earliest change consists in marked distension of the capillaries and venules, first in the submucosa and subsequently in the mucosa

Mann (1939) described the type of ulcerations which are usually seen as an acute lesion as follows they begin as a haemorrhage in the submucosa and the ulceration of the mucosa appears secondarily to the vascular injury The lesions rarely extend deeper than the submucosa and they become chronic or perforate only very infrequently

Key (1950), who studied the vessels of peptic ulcer by microradiography, observed that the acute ulcer presents a picture of an acute vascular disturbance chiefly occurring just under the mucous membrane—a hypervascularity and derangement, an increase in vessels and no ischaemia

The chronic ulcer

The *chronic* callous ulcer (the "ulcus simplex rotundum of Cruveilhier) differs in all respects from the acute ulcer Typically the chronic ulcer is invariably single although two independent chronic lesions in proximity are

sometimes encountered and may co exist with one or more scars of former chronic ulcers The simultaneous occurrence of chronic ulceration or scarring of the stomach and duodenum is infrequent and is considered by Stewart (1929) as an indication of important aetiological difference The chronic ulcer is much larger than the acute one and may reach enormous dimensions it occurs mostly on the lesser curvature Microscopically the margin of the ulcer is no longer seen to be sharp, but is thickened, rounded and overhanging, the edges are oedematous, indurated and usually red and inflamed The mucosa terminates abruptly at the edge of the crater is usually congested and haemorrhagic and there is a great increase in the lymphoid tissue on both sides of the muscularis mucosae The submucosa is much thickened and the muscularis is invariably completely breached which is one of the most characteristic features of the chronic ulcer The floor is formed by fibrous tissue which may be adherent to an adjacent viscus and the serosa is thickened and opaque over an area considerably larger than that of the ulcer Askanazy (1920) described the typical structure of the floor of a chronic ulcer as consisting of four distinct layers (*a*) on the surface there is a zone of purulent or fibrinopurulent exudate in which neutrophil, polymorphonuclear cells are found in abundance mixed with fibrin, (*b*) a zone of fibrinoid necrosis which contains nuclear debris of leucocytic origin, (*c*) a zone of young proliferating granulation tissue which, according to Stewart (1929), contains eosinophil cells, and lymphocytes which occur rarely below the level of the fibrinoid zone, (*d*) a zone of fibrous scar tissue in which the muscles are destroyed the blood vessels are thickened, showing obliterative endarteritis and thrombosis, and the nerves, often little altered are preserved This description of the pathological anatomy of chronic ulcer has been generally adopted

Palmer, Schindler and Templeton (1938) stated that the clinical, gastroscopical and roentgenological evidence supports the concept of ulcer as a penetrative process beginning in the mucosa and invading the deeper layers of the gastric wall

Mann (1939) described the development of the chronic lesion as an ulcerating process always beginning at the surface of the mucosa At first all that can be seen is an oval or circular area covered with a homogeneous grey membrane Microscopical examination of the lesion at this stage shows that this membrane is very thin involving only the surface cells and that it is composed of mucosal cells in various stages of necrosis with leucocytes and erythrocytes With the exception of small regions of haemorrhage between the tubules just beneath the membrane the rest of the tissue appears normal According to Collins (1943) the minimal lesion of chronic ulcer which can be recognised grossly is focal ulceration involving only the mucosa

THE HEALING OF PEPTIC ULCER

The acute ulcer

The natural tendency of acute ulcers, whether of the stomach or duodenum is to heal rapidly and it is a general observation that in animals artificial

lesions, however produced, heal with the greatest readiness, the difficulty being to prevent them from healing Ulcers which involve only the mucosa or submucosa heal without leaving a permanent scar, but if the muscular coat has been involved a certain amount of fibrosis takes place which remains permanent in the form of a scar The rate of healing of acute ulcers varies from 1 to 2 mm per day Bolton (1913) stated that as soon as the edges of the mucous membrane are separated from the slough and all the necrotic portions of glands have been removed by the gastric juice, the cells lining the ducts and bodies of the glands commence to proliferate and cover the surface with a single layer first of flattened cells and later of cubical cells

The chronic ulcer

According to Bolton (1913) healing in chronic ulcer consists of filling up the crater by the growth of firm granulation tissue from the sides and base of the ulcer, by linear retraction of the sides of the ulcer with the approximation of the lateral surfaces, and by the ingrowth of newly formed epithelial tissue from the sides of the wound towards the crater

Mann and Williamson (1923) observed that the process of healing begins with the subsiding of the inflammatory reaction in and around the base of the defect and the sloughing off of the necrotic tissue on the surface of the base Many experimental workers have shown that as a chronic ulcer progresses there is continued connective tissue proliferation which limits its extent as well as prevents its perforation, the balance of power alternating between progression of the lesion and its healing

It is evident, according to Vines (1940), that a chronic ulcer must heal by granulation from below upwards and such a zone of granulation tissue is an almost constant histological feature

Longmire, Beal, Lippman and Bishop (1952) emphasized that an erosion heals by epithelial proliferation without scar formation, complete re-epithelization of 70–90 per cent of the gastric mucosa occurring in three weeks, whereas an ulcer heals by granulation and scarification

CLINICAL COMPARISON OF ACUTE AND CHRONIC ULCER

Macroscopic appearances

Inspection of the two types of ulcers shows marked differences which are reflected in their size, shape and number These differences are so striking that they must be accepted as significant

The *size* of the chronic ulcer is generally large while the acute ulcer varies considerably but is usually small, frequently too small to be visible to the naked eye The *shape* of the acute ulcer, depends upon the condition of the organ at the time of examination It may appear as a short, red, fissure which on stretching assumes an oval or rounded form, it is characteristically regular, while the chronic ulcer is subject to considerable variations and is markedly irregular in shape The chronic ulcer is usually single very exceptionally two or more ulcers may be present the ' kissing ulcer being probably an

extension of the original ulcer or the result of direct irritation produced by it The acute ulcer is multiple, the number varying within considerable limits

Location

The location of the chronic gastric ulcer is a matter of considerable importance Stewart (Hurst and Stewart, 1929) in a series of 210 post mortem cases found 172 (82 per cent) of chronic ulcers located on the lesser curvature 26 (12 per cent) in the pyloric canal 2 (1 per cent) in the cardia 4 (2 per cent) on the anterior wall and 6 (3 per cent) on the posterior wall, in a surgical series of 170 cases 164 (96 5 per cent) were located on the lesser curvature and 6 (3 5 per cent) in the pyloric canal This marked preponderance of the chronic lesion occurring in the neighbourhood of the lesser curvature has suggested the term gastric pathway or Magenstrasse" (Waldeyer, 1908)

In marked contrast the acute ulcer may be found in any part of the stomach and no special significance can be attributed to its location

In duodenal ulcer, the location of the acute lesion is similar to that of the acute gastric lesion—there is no specific location—but in the chronic duodenal lesion it is invariably confined to the first part of the duodenum

Symptomatology

There is a most striking and fundamental difference between the symptomatology of the acute and chronic ulcers

The acute ulcer is devoid of all clinical manifestations It may be recognized as a chance occurrence during a gastroscopic examination It becomes manifest only through the sudden and dramatic appearance of one of its complications—haemorrhage or perforation Symptoms of malaise, a slight rise of temperature and increased pulse rate may usually be elicited retrospectively These signs are the general body reaction to a toxic agent The activity of the ulcer is invariably short in duration, whether it is fatal (through the consequences of its complications), or whether it heals pain being conspicuous by its absence The chronic ulcer, in contradistinction is insidious in onset and is marked by a long history of dyspepsia but without general body reaction Pain appears with clockwork regularity and is recognized to be pathognomonic

Inflammatory reaction

The inflammatory reaction which accompanies both types of ulcer has important differences In the acute ulcer which is necrotic in nature the inflammation is circumscribed and forms a very narrow border round the ulcer The inflammatory reaction of chronic ulcer varies from a slight increase in the substance of the mucous membrane giving rise to the so-called état mamelonné to areas of intense inflammation If the irritation persists it may lead to hypertrophic chronic gastritis, duodenitis or pyloritis Diffuse inflammation is invariably present with chronic ulcer Furthermore in contradistinction to the acute ulcer the inflammatory exudate of the chronic ulcer contains

neutrophil polymorphonuclear cells (Askanazy, 1920) while the layer of proliferating granulation tissue contains eosinophil cells, lymphocytes and plasma cells (Stewart, 1929) Boyd (1942) states that when examining a series of chronic ulcers one is impressed by the signs of active inflammation which are found even in the least active looking specimens Chronic inflammation is frequently present in conditions which show a symptomatology identical with that of chronic ulcer, although no actual lesion can be demonstrated It should be *emphasized that whereas the chronic ulcer makes its appearance* in an inflamed, diseased part of the affected organ, the acute ulcer occurs generally in a part of the stomach which is healthy and shows no sign of antecedent disease

Attention must also be drawn to the element of infection as related to ulcer While in the acute ulcer there is generally an intimate connection with some infective or toxic element, in the chronic ulcer infection plays only a secondary role, if at all, Hayem (1911) has emphasized that the presence of organisms on the surface of the chronic lesion is of no consequence, but when the microbes reach the gastric wall through the circulation, it is of serious import

The association of hydrochloric acid with ulcer

It is generally recognized that the chronic peptic ulcer is associated with increased acid values (Hurst and Stewart, 1929) and that when there is no acid, there is no ulcer (*Schwartz, 1910, Palmer and Heinz, 1934) On the* other hand, in acute ulcer the acid values may be normal, frequently reduced or may even be absent They may occur in the presence of histamine resistant achlorhydria (Palmer and Nutter, 1940)

Conclusions

From these fundamental differences, the conclusion may be drawn that *the acute ulcer and the chronic ulcer are produced by the action of primarily* different mechanisms, and are therefore, aetiologically independent entities The conception that a chronic lesion begins its existence in the form of an acute lesion and acquires its chronicity by the persistence in the activity of the original morbid process may appear superficially self evident, but has no evidence to support it To affirm that a chronic ulcer originates from an acute ulcer is to misapply the nomenclature as well as to misinterpret the evidence The life history of the chronic ulcer may be visualized as beginning with a chronically inflammed and, *therefore diseased* mucous membrane the persistence of the original morbid process leading to the initial breach of the mucosa and preventing it from healing Thus there are two stages in the development of the chronic ulcer, the appearance of the inflammatory reaction, and the breakdown of the mucous membrane In other words, the chronic ulcer is ' chronic' before it becomes an ulcer" The acute peptic ulcer never becomes chronic nor has the chronic peptic ulcer ever been acute

RELATION OF ULCER TO OTHER DISEASES

It is proposed first to investigate the acute form of the ulcer to show that it represents a secondary manifestation systemically transmitted of a remotely situated morbid condition The chronic form of ulcer will then be studied in order to show that it represents a primary manifestation in response to a local irritation

Acute ulcer

The association of the acute ulcer with some active pathological condition situated at a point remote from the ulcer strongly suggests that the acute ulcer is a secondary manifestation and is the result of some associated infective or toxic state The primary condition may be situated at some distance from the ulcer and is usually of a chronic nature the acute lesion being produced systemically through some embolic process Rokitansky (1842) pointed out that acute erosions are associated with the most varied acute and chronic illnesses such as poisoning chlorosis, cerebral disease, anaemia, eclampsia burns trauma, infections and septic processes in general Brinton (1864) observed that the acute lesion is associated with a large number of diseases "in proportion much more akin to those of their known frequency than to any other of their circumstances Dieulafoy (1897–98) who noted small or large elevations of temperature with acute ulcerations stated that with few exceptions the pathogenic process responsible for their causation (haemorrhagic erosions) is the result of a toxic infection Hayem (1911) pointed out that while the acute ulcer is associated with a diversity of pathological conditions there are many procedures which, similarly, reproduce the experimental ulcer, and the aetiology of acute ulceration is striking by its richness and its variety Bolton (1913) stated that there appears to be very little doubt that many cases of acute ulcer which have been described as occurring in various non infective diseases such as heart disease, liver or kidney disease, are really due to a secondary invasion of the body by micro-organisms He pointed out that it is not only in general septicaemic diseases that acute ulcer of the stomach arises but also in conditions where a local septic focus is present

He emphasized that the sudden haemorrhage which occurs without any previous warning is generally accompanied by a rise in temperature and that when sudden perforation is the first clinical manifestation of the disease it is definitely of infective origin Greggio (1916) considers that all ulcers of the newborn are acute and are a secondary manifestation of a primary septic condition

According to Moutier (1926), erosions occur in toxaemias septicaemias and common gastritis Stewart (1929) tabulated 12 different conditions associated with 151 cases of acute gastric and duodenal ulcer and in these practically all could be due to an infective cause while Kellogg (1933) gave 20 different items which he classified under the headings of (*a*) corrosive

poisons, (*b*) ulcer of metabolic or infectious origin, (*c*) septic processes, and (*d*) infectious diseases

Curling's ulcer

The ulcer which follows burns as a complication and is generally referred to as Curling's ulcer helps to some extent to elucidate the pathological process of the acute peptic lesion

Greenwood (1880), Perry and Shaw (1893), Broadbent (1908), Moynihan (1912), Robertson and Boyd (1923), Stallard and Borman (1928), Harris (1929), Pack and Davis (1930), and Maes (1930), attributed the cause of Curling's ulcer to sepsis or toxins It is significant that the ulcers do not develop until 10–14 days after the burn and that frequently symptoms appear only 24 hours before death Harkins (1938) has shown experimentally that when dogs died or were killed within 24 hours of burning there was no ulcer present and no congestion of the stomach

Hartman (1946), who produced third degree burns in dogs, reduced the incidence of ulcers from 77 7 to 23 per cent by the administration of penicillin This was clinically confirmed by Braithwaite and Beales (1949) Wilson (1935) and Hartman (1945) observed that patients with burns do not show excessive gastric acidity Necheles and Olson (1942) found that there is an excess of gastric secretion which, according to Palmer (1942) and Behrmann, Schelling and Hartman (1946), is induced by the presence in the blood of histamine or a histamine like substance This substance had been demonstrated by Rosenthal (1937) Friesen (1950) stated paradoxically that "whereas mucosal congestion is the predisposing factor, gastric acidity is undoubtedly the precipitating agent in ulcer formation following burns, which does not necessarily imply that hyperacidity or hypersecretion occurs in burns It is pertinent here to add that in the experiments in which dogs with gastric pouches were subjected to burns, no increase in gastric acidity or secretion was noted "

Increased concentration of haemoglobin was observed by Underhill, Carrington, Kapsinow and Pack (1923), Friesen and Wangensteen (1946), Brooks, Dragstedt, Warner and Knisely (1950) and Friesen (1950), and involvement of adrenals by Weiskotten (1917) and Harkins (1938) Adreno-cortical hyperactivity with marked eosinopenia was observed by Sevitt (1954)

The acute ulcer as a manifestation of the 'alarm reaction

Selye (1940) has shown experimentally that the acute ulcer is the result of the response produced by the 'alarm reaction which he described Selye (1937) stated in his Studies on Adaptations that the alarm reaction represents a non specific response of the organism to damage as such Its main symptoms are adrenal enlargement, involution of the lymphatic organs, degeneration and death of cells in various tissues ulcer formation in the digestive tract, and oedema formation These symptoms are the same whatever the specific nature of the damaging agent may be Drugs, surgical injuries, spinal shock excessive muscular exercise, all elicit the same reaction Experiments on rats show

that if the organism is exposed daily to a stimulus causing an alarm reaction in the beginning, it will eventually become adapted to this stimulus This adaptation however, is lost after some time, apparently because the organism runs out of something needed for the fight against the damaging agent At this time the animals die in a condition of exhaustion, with symptoms similar to those seen in the acute stage of alarm The whole reaction of adaptation consists, therefore of three stages the stage of alarm, the stage of resistance, and the stage of exhaustion Gastric and intestinal ulcers appeared, histologically, to be due to complete dissolution of the mucosa and they are often accompanied by inflammatory infiltrations in the submucosa and muscularis

Selye and MacLean (1944) showed that the acute gastric ulcer, which occurs in man as well as in animals following exposure to various noxious agents (toxic doses of drugs cold, exhausting muscular work, surgical shock and other causes) is not due to any of the specific properties of these agents Apparently they are part of the response to the non specific damage caused by these stimuli and represent one of the symptoms of the "alarm reaction

Steiner (1946) who performed necropsies on Okinawans during the second world war found no disease of the stomach except ulcers, these were acute and were related to psychosomatic stress following bombing and invasion They were incidental post mortem findings but no healed peptic ulcer scars were found McDonnell and McKloskey (1953) examined the records of 1,781 consecutive autopsies (performed during 1945–1950) following surgical procedures, they found that of 243 cases in which death occurred within two months of operation (performed on other than central nervous system lesions) 8 (3 24 per cent) had acute peptic ulcers Similar ulcerations were shown in 5 (2 7 per cent) of 179 patients in whom central nervous system lesions were found at autopsy According to these authors it seems probable *that the acute peptic ulcers associated with surgical procedures* burns and intracranial lesions are a result of the body s exposure to stress

Chronic ulcer

The association of acute ulcer with an acute inflammatory lesion (for example acute appendicitis) on the one hand and the association of chronic ulcer with a chronic inflammatory lesion (chronic appendicitis) on the other hand suggests a parallelism in the pathogenesis of these diseases

In this section it will be shown that the relationship of chronic ulcer to chronic appendicitis is entirely different from the relationship of acute ulcer to acute appendicitis and that the mechanisms involved are not the same

Moynihan (1910) and Paterson (1910) *drew attention to the diseased* appendix as a cause of gastric symptoms associated with hypersecretion, hypermotility and pyloric spasm Wilkie (1914) suggested that toxic absorption from the appendix or colon could produce an irritable condition of the autonomic nervous system with a tendency to ulcer formation In a series of 718 cases of duodenal and gastric ulcer, Moynihan (1923) removed the appendix 307 times and the gall bladder 23 times In more than 50 cases the gall bladder or the appendix or both had previously been dealt with by

poisons, (*b*) ulcer of metabolic or infectious origin, (*c*) septic processes, and (*d*) infectious diseases

Curling's ulcer

The ulcer which follows burns as a complication and is generally referred to as Curling's ulcer helps to some extent to elucidate the pathological process of the acute peptic lesion

Greenwood (1880), Perry and Shaw (1893), Broadbent (1908), Moynihan (1912), Robertson and Boyd (1923), Stallard and Borman (1928), Harris (1929), Pack and Davis (1930), and Maes (1930), attributed the cause of Curling s ulcer to sepsis or toxins It is significant that the ulcers do not develop until 10–14 days after the burn and that frequently symptoms appear only 24 hours before death Harkins (1938) has shown experimentally that when dogs died or were killed within 24 hours of burning there was no ulcer present and no congestion of the stomach

Hartman (1946), who produced third-degree burns in dogs, reduced the incidence of ulcers from 77 7 to 23 per cent by the administration of peni cillin This was clinically confirmed by Braithwaite and Beales (1949) Wilson (1935) and Hartman (1945) observed that patients with burns do not show excessive gastric acidity Necheles and Olson (1942) found that there is an excess of gastric secretion which, according to Palmer (1942) and Behrmann, Schelling and Hartman (1946), is induced by the presence in the blood of histamine or a histamine like substance This substance had been demonstrated by Rosenthal (1937) Friesen (1950) stated paradoxically that "whereas mucosal congestion is the predisposing factor, gastric acidity is undoubtedly the precipitating agent in ulcer formation following burns, which does not necessarily imply that hyperacidity or hypersecretion occurs in burns It is pertinent here to add that in the experiments in which dogs with gastric pouches were subjected to burns no increase in gastric acidity or secretion was noted "

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THE SUBNUTRITIONAL ULCER

An unusual form of ulcer connected with basic nutritional requirements has been seen in Europe as a post war phenomenon In the East chronic lesions are seen in populations exposed to severe food restrictions imposed by religious or other reasons, particularly in the consumption of proteins and during periods of grave famine The high incidence of gastric ulcer amongst Abyssinians and the Hindus of Southern India is well known (McCarrison, 1921) Hamperl (1932) who studied the sudden steep increase in the incidence of peptic ulcer ('Ulcusepidemie ') in the U S S R during the famine years of 1920-1922 stated that the inhabitants of Leningrad received a diet with the following average daily calories 1914, 2 300 calories, 1917, 1,760 calories, 1918 1,300 calories 1919, 800 calories 1920, 700 calories The increase in incidence was in direct proportion to the reduction of the food intake Ehrmann (1942) states that observations based on 15 000 autopsies and 7,000 hospital patients with peptic ulcer at the time of deficient nutrition in Germany during World War I, showed there was a marked increase in the incidence of peptic ulcer

There is considerable experimental evidence to support the view that dietary alterations are the cause of these ulcers Turck (1906) reported that ulcers occurred in animals simply by keeping them in close confinement until they were debilitated Ivy (1920) was particularly impressed with the fact that inanition or cachexia in an animal predisposes some of its cells to digestion and leads at times, to the formation of ulcers McCarrison (1921) showed that pigeons and monkeys kept on an exclusive diet of autoclaved rice or milk showed considerable pathological changes in the bowel The stomach in pigeons was atrophied and averaged 3 5 grammes in weight as compared with the original weight of 5 7 grammes

(See also Experimental Ulcer produced by deficiency states, p 146)

The "war" ulcer

The subnutritional ulcer as a war manifestation has been observed in the countries where low protein rationing was in force It is intimately related to the hunger oedema which occurred in World War I and produced disastrous consequences for its victims before the aetiological factor was recognized In World War II hunger oedema appeared in the occupied countries as well as in Germany Martin and Demole (1943) considered that it was the consequence of a deficiency of animal proteins Govaerts and Lequime (1943) related it to the osmotic pressure of the low plasma proteins

It is obvious that as hunger oedema affects all the organs of the body the muscle wall of the stomach will show less local resistance and will be more vulnerable to physical trauma and more liable to injury

Henning and Czerwensky (1944) described 90 cases of "Kriegsulkus as a war conditioned peptic ulcer which occurred on the small curvature of the stomach almost exclusively in males and more particularly in workmen engaged on heavy work

Kowalewski (1947) reported the results of his investigations made on Polish

operation and he stated that in many of the patients from whom he removed the appendix he felt that the obvious and sometimes gross disease antedated the development of the ulcer or ulcers in the stomach or duodenum, and consequently he regarded it as a primary source of infection Alvarez (1929) found gall bladder disease in 8 5 per cent of male gastric ulcer patients and in 13 3 per cent of female patients In the duodenal ulcer patients, 11 per cent of the men and 27 per cent of the women had associated disease of the gall bladder

Braithwaite (1923) has suggested that the flow of lymph from the ileo caecal angle may have some bearing on the cause of duodenal and gastric ulcer and he mentioned that, on abdominal section, the diseased appendix may be diagnosed whilst it is well out of sight by the following stigmata (*a*) pyloric spasm, (*b*) pyloric congestion, and (*c*) enlargement of glands on the greater curvature of the stomach and pylorus

These phenomena can be explained on the basis of the "ileogastric reflex" which has been shown (in the previous section) to be a manifestation of reverse peristalsis produced by obstruction in the region of the ileo-colic angle

THE CO EXISTENCE OF ACUTE AND CHRONIC ULCER

The conception that the acute and chronic lesions are unrelated disease entities is supported by the observation that the acute and the chronic ulcer can co-exist as unrelated phenomena in the same stomach Dieulafoy (1897–98) has suggested that the *exulceratio*—the superficial ulceration—may be grafted on to a chronic ulcer and display its own independent characteristics in the substance of the chronic lesion

Hayem (1911) has made it clear that the co existence of acute and chronic lesions which is occasionally seen is explained by the fact that the ulcer is old but the erosions are new and that it is essential to take the clinical history into account when interpreting these observations Bolton (1913) stated that in some cases the acute ulcers have healed, leaving scars, so that in the same stomach there may be active acute ulcers scars of acute ulcers and chronic ulcers He emphasized that the association of acute and chronic ulcer may be quite accidental, the acute ulcers being the result of some infective process which has attacked the person with chronic ulcer Duval (1924) in studying the "contemporary occurrence of chronic and acute ulcer, specifically refers to the infection which develops secondarily to a remote primary lesion or in a lesion which was originally sterile and he points out that fever and leucocytosis with an increase of polymorphs is particularly common in haematemesis and melaena, he also observed acute inflammatory lesions which complicated the process of chronic ulcerations found in pathological specimens

Stewart (Hurst and Stewart 1929) in a series of 4,000 autopsies found that 6 out of 89 (6 7 per cent) had both acute and chronic gastric ulcers and 18 out of 153 (11 8 per cent) both acute and chronic duodenal ulcers

nutrition, devitalization) and those which lead to the persistence or non-healing of such ulcers

Hauser (1926) stated that although it is correct theoretically not to separate the pathogenesis of erosion and ulcer and although even the smallest erosion can be considered as an ulcer, nevertheless the lesions have fundamentally different modes of healing, different clinical manifestations and different aetiologies There is also a lesion which exhibits the characteristics of both and it is the subacute ulcer which represents the transition from the acute to the chronic lesion According to Stewart (Hurst and Stewart, 1929) the sub acute ulcer represents a transitional stage, probably a short one, from acute to chronic ulcer Their number, size, position, naked eye and microscopic characters as well as their course, complications and sequelae occupy a posi tion intermediate between the acute and chronic lesions He stated further that since the process is a continuous one, sharp delineation into three categories of acute subacute and chronic must obviously be somewhat artificial and arbitrary, and it is difficult if not impossible, to apportion anything like precise time limits to the various stages

According to Konjetzny (1930) the *chronic ulcer starts as an erosion* situated in an inflamed gastric mucous membrane, and this view is supported by Palmer, Schindler and Templeton (1938–39) who stated that the morbid process begins in the mucosa, penetrates the submucosa and then the muscularis Eusterman and Balfour (1935) considered that subacute gastric ulcer in a clinical sense implies a subacute exacerbation of a chronic ulcer Moutier (1935) has never seen an intermediate form between the flat ulceration and the deep loss of substance gastroscopically and thought it exceptional to observe a typical ulcer or an aphtoid gastritis, or the trans formation of an erosion into a callous ulcer According to Zweig (1936) there is no gastroscopic evidence to show the transition from an erosive gastritis to a true chronic ulcer Schindler (1937) made 65 gastroscopic examinations on one patient over a period of ten years and though on each occasion he saw numerous erosions in the stomach a chronic gastric ulcer never resulted Dible (1937) pointed out that the small superficial acute ulcers and haemor rhagic erosions throw little light upon the real problem of the indolent chronic ulcer and that it is clear that chronic ulcer is dependent upon quite different factors from those which occasion the multiple erosions

Ivy, Grossman and Bachrach (1950) mention that in the classification of ulcers some authors include the third intermediate type of subacute ulcer They attempt to avoid the difficulty of its definition by saying (p 15) that

A subacute ulcer is intermediate between a healing acute ulcer and a definite chronic ulcer It represents an acute ulcer, the healing of which has been slightly retarded The submucosa about the margin is somewhat thicker than in an acute healing ulcer the margin is undermined in some regions and healing is present in others the eosinophils are absent or few It is not an acute ulcer, yet one hesitates to call it a chronic ulcer it is really an ulcer of slight chronicity

To contend that a subacute ulcer is a mixture of healing acute ulcer which

officers in German prison camps during 1941–1944 There were 1,890 cases and their ages ranged from 20 to 56 years with an average of 32 years He found that complete achlorhydria, after a test meal, occurred in 2 6 per cent in 1941, in 6 per cent in 1942, in 12 per cent in 1943 and in 14 8 per cent in 1944 Free hydrochloric acid on fasting was not found in 1941 in 17 8 per cent and in 1944 in 42 2 per cent of the cases The author concluded that insufficient food, both quantitatively and qualitatively, was responsible as this was largely composed of vegetables and was lacking in animal protein

According to Henning (1949) the "war" ulcer disappeared in the year 1947, an observation which was also confirmed by Markoff He also quotes Alpern of Charkov, who observed "war" ulcer in Russia

THE SO CALLED "SUBACUTE" ULCER

It is wrongly assumed that the chronic ulcer originates as an acute ulcer and that the period of transition is represented by the so called subacute ulcer, although there is no direct evidence to support this view

Cruveilhier (1839) considered that ulceration and ulcers of the stomach are consecutive stages of a single morbid process which eventually lead to perforation (It should be pointed out that the distinction made by French authors between "ulceration" and "ulcer" corresponds to "exulceratio" and "ulcus" or "acute and 'chronic' peptic ulcer respectively) He believed that the superimposition of inflammation on a haemorrhagic erosion could produce a small ulcer This view was supported by Rokitansky (1861), but rejected by Langerhans (1891) Neumann pointed out the importance of considering acute and chronic ulcers as separate entities Hayem (1911) emphatically rejected the contention of Cruveilhier and his followers that the depth of the lesion is the criterion which determines whether the lesion is an acute or chronic ulceration and he concluded that 'the pathogenesis established the nosology' He made it clear that acute ulcerations are 'mortifications of the gastric wall produced by various processes which have no relation to any disturbance of the secretory function of the stomach, through their origin, their anatomical constitution and the manner in which they evolve He pointed out the association of acute ulceration with a diversity of pathological conditions and the facility with which an experimental ulcer can be reproduced by multiple unrelated procedures and that these two general characteristics by themselves should be sufficient to differentiate these lesions from chronic ulcer

Aschoff (1921, 1924) stated that haemorrhages which are limited to the mucosa are the initial stage of the ulcus simplex of Cruveilhier and he believed that a chronic lesion may occasionally develop from an uncomplicated erosion, but that the cause of the erosion is not necessarily the cause of the ulcer Stewart (1923) argued that as all chronic ulcers arise in and from an acute ulcer, two aetiological problems are presented (*a*) the cause or causes of acute ulcer, and (*b*) the factors which lead to the persistence or non healing of such ulcers The various factors clinical and experimental, concerned in the production of chronic ulcer are those which act by producing injury (mal-

An interesting illustration of the problem was provided by Avery Jones in 1951 at the Festival of Britain Symposium at the Royal Society of Medicine, London when he showed gastroscopic drawings of a middle aged woman who was admitted to hospital for a suspected chronic ulcer Gastroscopic examinations revealed first a submucous haemorrhage, later its transformation to a superficial ulcer, and later still the healed ulcer, the whole cycle having been completed within a fortnight The usual orthodox treatment of chronic ulcer had not the slightest effect on the evolution of the acute lesion

It may be stated, in conclusion that there are three fundamental objections which militate against the theory of the transformation of the acute peptic ulcer into the chronic peptic ulcer (*a*) The first objection concerns the terrain in which the lesion occurs, that is to say the condition of the mucous membrane It is an accepted fact that the mucous membrane in which the chronic ulcer is located is chronically inflamed before the appearance of the ulcer and that the inflammation disappears only after the ulcer has healed On the other hand the acute ulcer appears either on a normal or atrophic mucous membrane which shows few signs of inflammation other than those associated with the trauma of the lesion In order to allow for the sequence of events which occur in the development of the chronic lesion it would be necessary to show that a complete change of the substratum takes place after the acute lesion has appeared There is no evidence which justifies this possibility (*b*) The second objection concerns the acid factor It is generally accepted that hydrochloric acid plays an essential role in the causation of chronic ulcer but takes no part in the causation of the acute ulcer Since the acid factor is present at the initiation of the lesion that is to say there is hyperchlorhydria and since the acid values with the acute ulcer are normal or more frequently subnormal in other words there is hypochlorhydria, in order to show that this transformation from hypochlorhydria to hyperchlorhydria takes place during the recognized short life history of the acute ulcer it would be necessary to postulate that a new mechanism is brought into action which effects this transformation There is no evidence that two mechanisms are concerned in the causation of the chronic lesion (*c*) The third objection—the most important—concerns the focus of origin of the ulcers It has been shown conclusively that on the one hand the acute ulcer starts in the submucosa (Hayem 1911 Redwitz and Fuss 1928 Boles Riggs and Griffiths 1939, Mann 1939 and Key 1950) and, on the other hand the chronic ulcer starts on the surface of the mucous membrane (Askanazy 1920, Redwitz and Fuss 1928 Stewart 1929, Newcomb 1932 Palmer Schlinder and Templeton 1938, Collins 1943 Albot and Debray 1946 and Key 1950)

It is reasonable therefore to conclude that the acute ulcer does not become chronic and the two types of ulcer must represent two independent and unrelated disease entities

at the same time tends to become a chronic ulcer, is to confuse the evidence Healing of an acute ulcer begins almost coincidentally with its formation because the causative factor ceases its activity soon after the initiation of the lesion Healing of the chronic ulcer takes place simultaneously with the progression of the lesion, a constant attempt at healing occurs while the factor responsible for its causation persists, it is the balance of these two opposing forces which determines the final issue

Ivy, Grossman and Bachrach (p 174) also say that many observers came to consider chronic peptic ulcer as a separate disease but paid little attention to the nature of the acute lesion "More recently all students of the problem have favoured the view that the chronic ulcer is initially either an acute ulcer or an erosion Thus the two opposing hypotheses regarding the origin of peptic ulcer are (1) a chronic peptic ulcer does not originate from any of the acute lesions seen in surgical and autopsy specimens of the stomach, duodenum or jejunum, (2) a chronic peptic ulcer always originates from an acute lesion, which may be (*a*) any type of acute ulcer or (*b*) only a certain type of acute ulcer' They then proceed to declare that "it is difficult to conceive, and no one has explained adequately, how a chronic ulcer could arise, like Minerva springing fully armed from the forehead of Jove, without its being initially an acute lesion of the mucosa Even if an ulcer arose as a result of the alleged withdrawal of the trophic effect of nerve impulses on the cells of the mucosa, an acute lesion would occur" The evidence is examined to support the assumption that a chronic ulcer arises as an acute lesion by reference to the co existence of acute and chronic ulcer, acute lesions in infectious processes acute lesions in burns, occurrence of chronic ulcers at the site of experimental acute ulcers They then state emphatically that a primary breach of the epithelial surface (mucosa) is a *sine qua non* of a chronic ulcer A multiplicity of factors may operate to impair the mucosa by decreasing the protective mechanism or by increasing the action of aggressive factors on the mucosa so that an erosion, or an acute ulcer, or both develops However, towards the end of their exposition they temper their dogmatism by stating that 'the experimental evidence from laboratory and the descriptive evidence from surgery and necropsy presumptively establishes that the "chronic ' peptic ulcer in man originates from an acute erosion or ulcer of a non specific type ' They then surprisingly, admit that under ordinary conditions erosions and acute ulcers of the stomach and duodenum heal rapidly, in fact so rapidly that it is remarkable that a chronic ulcer ever occurs It is indeed highly significant that as yet no suggestion has been forthcoming to explain how, of all the multiple acute ulcers, one particular ulcer is singled out to be "transformed into a chronic ulcer, while all the others heal rapidly and disappear without leaving a trace of their existence and the possibility is ignored that the chronic ulcer is the final breakdown of an inflamed mucous membrane thus being 'chronic' before being ulcer

Selye (1951) stated that ' there was no proof that the acute gastric erosion of the alarm reaction would tend to become chronic and transform itself into a peptic ulcer'

rhythm) and food, comfort, pain for duodenal ulcer (triple rhythm) has no special significance apart from the location of the lesion This difference of rhythm, however, is not rigorously true

Ivy, Grossman and Bachrach (1950) stated that despite the differences their similarities are very marked The gross appearance of the lesions—allowing for differences of anatomical location—the symptoms the life history of the individuals with the disease, the complications and sequelae, the responses to surgical and medical therapy, all point to a fundamental identity of gastric and duodenal ulcer

Grossman (1951) pointed out that in spite of the difference in acid secretion curves, it is of special importance to the consideration of aetiological factors that clinically and experimentally, gastric and duodenal ulcers occur coincidentally and experimentally in the same man or animal with significant frequency

These ulcers are sufficiently similar in many of their characteristics to justify the comprehensive term of gastro-duodenal ulcer

Conclusions

The study of the pathological anatomy of peptic ulcer in conjunction with its clinical manifestations shows clearly the fundamental differences which distinguish the acute and chronic lesions A comparison of their morbid anatomy discloses the difference in their number size, position distribution macroscopic and microscopic appearance, origin, course healing complications and sequelae while a comparison of their symptomatology discloses the difference in the age and time factors, the secretory and motor reactions their association with gastritis and with pain. All these observations indicate that the difference of the lesions is not one of degree but of kind and that the lesions are not sequential stages in the evolution of one disease complex but are two different disease entities unrelated to each other

It is evident that the causation of the ulcerative lesion involves two elements an active morbid process, and a time factor

The painless acute ulcer is an unforeseen isolated phenomenon which is fulminating uncontrollable and transient, and its appearance immediately determines its conclusion It reaches finality whether it heals or produces complications and the morbid process is exhausted almost at the moment of its inception It is the high virulence of the causative agent rather than the short time factor, which plays the preponderant role

The painful chronic ulcer displays a protracted life history without reaching an end stage of its evolution It is slow in development discloses a tedious symptomatology, but responds to treatment and is controllable It is main tained by a fluctuating alternating state of necrosis and repair and it is the long time factor rather than the virulence of the causative agent which plays the preponderant role

The acute ulcer is a secondary manifestation caused by a morbid process situated at some distance from the gastro-duodenal lesion The chronic ulcer is a primary manifestation representing the natural reaction to a local irritation

ASSOCIATION OF GASTRIC AND DUODENAL ULCER

According to Feldman (1953), data collected from different sources revealed the association of gastric and duodenal ulcer as follows autopsy incidence, 0 32 per cent, x ray incidence, 0 15 per cent, surgical incidence, 7 per cent He observed that of 383 cases of peptic ulcer at autopsy 25 showed the association of gastric and duodenal ulcer, an incidence of 6 5 per cent

The anatomical and physiological unity of the stomach with the first part of the duodenum has been studied in Chapter 4 p 80

The pathological identity of the ulcers and the clinical identity of the symptoms will now be examined

Pathological identity of the ulcers

There is a striking similarity linking gastric and duodenal ulcers The acute and chronic lesions which occur in the stomach have corresponding lesions in the first part of the duodenum Perry and Shaw (1893) noted that out of 120 patients with duodenal ulcer, 15 presented concomittant ulcers in the stomach Moynihan (1912) observed that duodenal ulcers may extend into the stomach and thus form a pathological link between them Hart (1918–19) believed that, in view of the marked similarity of duodenal and gastric ulcer, a uniform, if not always the same, aetiology must be accepted Enriquez and Gaston Durand (1924) insist that there is no duodenal syndrome as opposed to a gastric syndrome but there is a common dyspeptic syndrome for the affections of the stomach and duodenum Palmer (1926) and Bolton (1928) consider that the mechanism of pain in gastric and duodenal ulcer is essentially the same According to Crohn (1927) both acute and chronic ulcers of the duodenum are similar in their origins and characteristics to analogous forms of lesions of the stomach Bolton (1928) has shown that nearly 80 per cent of the acidity curves obtained from cases of duodenal ulcers are of the pyloric ulcer type and that 90 per cent of the curves of acidity of pyloric ulcers show similar curves Hunter (1923) and Ryle (1926) have published figures which approximate with these findings Wellbrock (1929) has shown that the histological picture of chronic duodenal ulcer is similar to that of chronic gastric ulcer and he has emphasized that the typical, true, duodenal ulcer and gastric ulcer are identical lesions Berg (1930) Eustermann and Balfour (1935) and Present (1938), held similar views

Clinical identity of the ulcers

The symptomatology of chronic gastric and duodenal ulcers is the same In both the acute lesion cannot be diagnosed except by its complications—haemorrhage and perforation The characteristic features of peptic ulcer pain chronicity periodicity, quality and relation to food which are pathognomonic of the lesion are essentially the same in both varieties of the disease Moynihan (1923) has drawn attention to the periodicity of the pain which is altered by variations in the quantity and quality of the food and by the irregularity of the meals The variation of the rhythm of the pain in relation to food food, comfort, pain comfort for gastric ulcer (quadruple

Jankelson (1945) in an analysis of 685 cases of upper digestive tract haemorrhage found 60 cases (9 per cent) of haematemesis which remained unexplained In 28 of these (45 6 per cent) there was no significant digestive history, in 9 cases (15 per cent) there was a brief history of mild epigastric discomfort, in 9 cases (15 per cent) the symptoms which lasted from 2 weeks to 3 months were bizarre and not suggestive of any pathological lesion, 6 cases (10 per cent) in which the symptoms lasted up to one year had com plaints which were not diagnostic Schiff and Shapiro (1951) found that in 34 of 339 patients with proved bleeding peptic ulcer there was no history of any digestive distress prior to the haemorrhage while in 70 the distress was atypical Cole (1951) found, in 25 per cent with massive bleeding no ante cedent history

Haemorrhage following emotional stress in patients with and without a history of ulcer has been described by many authors (Davies and Wilson 1939 Gainsborough and Slater 1946, Avery Jones, 1947)

Haemorrhage as a first symptom was reported as 6 8 per cent of 137 cases (Burger and Hartfall, 1934), 6 4 per cent of 154 cases of gastric ulcer and 2 2 per cent of 46 cases of duodenal ulcer (Kalk 1936) 14 1 per cent of 120 cases (Andresen, 1939), 9 6 per cent of 230 cases (Kirsner and Palmer, 1939), 20 per cent in 144 cases (Wollman 1941), 15 2 per cent of 283 cases (Rafsky and Weingarten, 1942), 10 8 per cent of 129 cases (Eads 1946) and 50 per cent of 140 cases (Wilkinson and Tracey, 1946)

It is of interest to note, as pointed out by Ivy, Grossman and Bachrach (1950) that the average of 16 2 per cent of haemorrhages as the first symptom compares well with 14 per cent of perforations as the first symptom of ulcer It has been suggested that in patients with gastric haemorrhage as a first symptom it is due to a "silent ulcer and that x ray examination may disclose a crater which causes no pain there is however, little evidence to support this view

Association of haemorrhage and infection

Post-operative gastric infection as a cause of haemorrhage was described by Billroth (1867) who found multiple erosions of the duodenum which he suggested were caused by sepsis following an unsuccessful attempt to remove an enormous struma Hutchinson (1911) observed that of gastric and intes- tinal haemorrhages which occurred after abdominal operations a severe septic infection was present in 80 per cent of the cases before the operation and that similar lesions of the stomach and duodenum are met with in certain cases of disease where no operation has been performed According to Bolton (1913) perhaps the commonest cause of haemorrhage into the (gastric) mucous membrane is bacterial infection either by direct action of the bacterial poison on the capillary wall or by giving rise to vascular occlu sion and haemorrhagic infarction Sherren (1924) found acute ulcers in all patients with digestive symptoms who died from haematemesis In 63 cases which he explored for acute ulcer 29 had definite disease of the appendix 27 of these had no further haemorrhage In 15 cases in which he removed the

CHAPTER 6

HAEMORRHAGE AND PERFORATION

The two complications of ulcer—haemorrhage and perforation—will be studied on parallel lines because the evidence supports the view that they are of similar aetiology, although they occur rarely at one and the same time, whether the lesions haemorrhage or perforate appears to depend more on the chance element of location and virulence of the active process than on other aetiological factors It is difficult to appreciate the significance of these manifestations without establishing their relationship to the original lesions It will then be seen that they assume a different meaning when they occur in association with the acute or with the chronic ulcer

HAEMORRHAGE

Gastro intestinal haemorrhage occurs in a great variety of diseases and may be produced by many causes The present study will consider only its relation to the ulcer problem

Incidence

It is difficult to ascertain with any precision the incidence of gastro duodenal bleeding as melaena may pass unnoticed, particularly in those patients who do not experience any pain Statistics on this subject are often contradictory and tend to give a false picture of the true position

Wilbur (1932) examined 602 cases of intrinsic gastro-duodenal lesions as causative factors of haematemesis and found that more than 85 per cent were due to peptic ulcer, including secondary ulcer

Rivers (1935) believed that 90 per cent of all duodenal ulcers bleed at some time Stolte (1944) found from an examination of the histories of 333 ulcer patients that except for the greater tendency to bleed in the first year and a lesser tendency after the tenth year of the disease, the frequency of bleeding is directly related to the duration of the disease According to Ivy, Grossman and Bachrach (1950) 23 7 per cent of gastric ulcers and 19 1 of duodenal ulcers bleed

Symptomatology prior to haemorrhage

Hellier (1934) reported that in 303 cases of haematemesis 96 had proved ulcers while 106 had a vague history and negative x ray findings Of the fatal cases 4 were acute 9 acute with scarring and 9 chronic gastric ulcers, 6 chronic duodenal ulcers and 2 chronic jejunal ulcers Moschcowitz Mage and Kugel (1941) pointed out that haematemesis or melaena, or both, without pain is common and that recurrences are the rule

Sex incidence

Sex incidence has also changed in an extraordinary manner since the second and third decade of this century, showing an overwhelming pre ponderance in the male sex Brinton (1857) observed 68 4 per cent in females in a collected series of 234 cases, Broadbent (1897) 86 per cent in 50 cases Brunner (1903) noted an incidence of females of 64 4 per cent in 423 cases Moynihan (1910) 26 9 per cent, Petren (1911) 48 per cent in 100 cases Morley (1913) 32 1 per cent in 112 cases Schoemaeker (1914) 52 per cent, Norrein (1915) 40 per cent in 105 cases and Hertz (1918) 39 5 per cent in 60 cases Speck (1923) observed 5 males and 14 females (73 6 per cent) for the period 1900–1910 and 41 males and 13 females (24 per cent) for the period 1911–1920 For the two years 1921 and 1922 there were 32 cases all males Meyer and Brams (1926) had 62 cases in 3 years also all males Schwarz (1925) reported 24 7 per cent females in 80 cases, and Dunbar (1926) 8 3 per cent in 387 cases

Bager (1929) in a collected series of the Swedish hospitals reported an incidence for 1911 of 26 males and 10 females, for 1916 of 65 males and 33 females but for 1925, 156 males and 30 females Dineen (1929) had a male incidence of 97 2 per cent in 142 cases Williams and Walsh (1930) 152 males in 158 cases Semb (1930) 135 (81 32 per cent) males in 166 cases, and Zukschwerdt and Eck (1931) 93 1 per cent in 117 cases, Blackford and Baker (1931) found only 43 females in 954 collected cases Graves (1933) 97 9 per cent males in 141 cases Scotson (1933) 94 per cent in 181 cases James and Matheson (1934) 84 per cent in 75 cases Schilling (1935) 84 9 per cent in 265 cases Thompson (1937) 94 2 per cent in 500 cases, McCreery (1938) 95 per cent in 170 cases Shawan (1938) 98 2 per cent in 227 cases Herzberg (1938) 93 7 per cent in 410 cases, and Judin (1939) 98 1 per cent in 1 355 cases Odom and De Bakey (1940) found 98 1 per cent in 211 cases Judin (1939) expressed the view that the disproportion in sex incidence points to the role of the female sex glands during their period of greatest activity De Bakey (1940) in a collected series of 14 339 cases found that 92 2 per cent were males According to Jennings (1940) prior to 1900 3 of every 6 perforations occurred in women 1 in an elderly woman and 1 in an elderly man McCabe and Mersheimer (1943) had 82 males in 89 cases Estes and Bennett (1944) 78 males in 80 cases Black and Blackford (1945) 92 males in 96 cases and Olson and Norgore (1946) in 166 cases had 95 8 per cent of males Baritell (1947) in 88 cases found 3 females or 2 93 per cent of the total as the average ratio of males to females was 3 31 to 1 the percentage figure of 2 93 may be adjusted to 9 7 Moore and Hendricks (1948) had 97 males in 101 cases there were 6 Negroes of whom 5 were males and 1 female Sure (1949) in 362 cases had 95 3 per cent males Turner (1951) reported 15 females in 185 cases

Age incidence

Relatively few cases of perforation occur in childhood and old age the great majority occur in the third fourth and fifth decades (De Bakey 1940)

of cases with perforated gastric ulcers increased more than tenfold as compared with peace time

Illingworth, Scott and Jamieson (1944) in a comprehensive study reported a rise in admissions of perforated peptic ulcer cases from 200 in 1929 to 600 in 1940 in an area where population changes had been minimal The incidence of perforated peptic ulcer appeared to have risen from 11 per 100,000 in 1924 to 25 per 100,000 in 1938 There was a marked rise during the war for the period 1940–41 followed by a return to a normal level The 1940–41 rise was not correlated with air raids in the area, but anxiety about the war situation, overwork and perhaps undernutrition may have been the cause

Kalk (1945) stated that a marked increase of perforation for the period of intense air attacks had been reported by Berg for Hamburg, by Lohmann for Berlin and by Hoffman for Cologne

Proportion of duodenal to gastric perforations

The proportion of duodenal to gastric perforations appears to have changed in recent years and there is now a marked preponderance of duodenal over gastric perforations Speck (1923) observed perforations in 17 gastric and 2 duodenal ulcers for the period 1900–1910, in 43 gastric and 11 duodenal ulcers for the period 1911–1920, and in 9 gastric and 23 duodenal ulcers for the years 1921–1922 Hurst and Stewart (1929) reported that in 180 autopsies in which gastric ulcer was present 36 per cent had perforated and in 313 autopsies with duodenal ulcer 56 per cent had perforated Williams and Walsh (1930) in 158 cases of perforation found 124 duodenal and 34 gastric ulcers, Scotson (1933) reported on 131 duodenal, 45 gastric and 5 anastomotic ulcer perforations Eliason and Ebeling (1934) reported in 545 duodenal ulcers 60 (11 per cent) and in 183 gastric ulcers 14 (7 6 per cent) perforations Roof (1934) had 20 4 and 18 per cent, and Present (1938) in 520 cases 26 and 15 per cent respectively, Schilling (1935), in 265 cases, had two thirds gastric and one third duodenal perforations Judin (1939) reported 90 per cent duodenal and 10 per cent gastric perforations Judin (1940) observed in his first series (for the years 1929–30) an incidence of 97 (84 7 per cent) duodenal ulcers in 118 perforations, in his second series (for the year 1932) 194 (91 6 per cent) in 212 perforations and in the six years to 1936, 288 (87 5 per cent) in 327 perforations Odom and DeBakey (1940) observed 92 gastric and 101 duodenal perforations Harrison and Cooper (1942) 51 duodenal and 6 gastric and McCabe and Mersheimer (1943) 10 gastric 42 prepyloric 10 pyloric and 25 duodenal Estes and Bennett (1944) reported the incidence as 63 duodenal and 16 gastric, Heuer (1944) as 40 duodenal and 17 gastric, Black and Blackford (1945) as 87 duodenal 6 gastric and 3 pyloric Moore and Hendricks (1948) had 17 in the duodenum and 84 in the stomach which were classified as 29 gastric, 42 prepyloric 9 pyloric and 4 at the cardiac end In Baritell s (1947) 88 cases 71 (80 7 per cent) were duodenal 9 (10 2 per cent)gastric and 8 (9 1 per cent) pyloric In Gilmour s (1953) series 160 (77 7 per cent) were duodenal 43 (20 8 per cent) gastric and 3 (1 5 per cent) stomal ulcers

chronic peptic ulcer occurs in the aged and that such patients die from the complication of haemorrhage and perforation of a chronic ulcer, their study directs attention to the occurrence of acute peptic ulcers in the aged Such acute ulcers may become chronic, but more often they result in acute haemorrhage and perforation causing the death of the patient Such acute ulcers may be primary, or secondary in association with acute febrile disease, gall bladder disease, operative procedure or cardiac failure The natural tendency in the aged to a diminution of secretion of hydrochloric acid and pepsin and the consequent diminution of appetite which produces a reduction in the intake of vitamins must also be taken into account

INCIDENCE IN THE YOUNG

In view of its intimate relation to infection, perforation in infants is dealt with in a subsequent section (page 128)

Seasonal incidence

It is difficult to draw any conclusion of the effect of the seasonal factor in gastro-duodenal perforations since there is much divergence in the reported observations

Broadbent (1897) found the greatest incidence in the period from October to March (which he ascribed to the greater prevalence of anaemia during winter), and Brunner (1903) mostly in November and least in July August Dunbar (1926) found little difference in the monthly frequency but the largest number occurred in January, then March, then July

Hinton (1931) found 44 7 per cent in 105 cases to occur in March April and October November, Eliason and Ebeling (1934) 32 4 per cent in October November and December Perforation occurred most frequently in the spring and autumn for Rhodes and Collins (1933), Juster (1935), Hull (1937) Sosnyakov (1937) in the autumn and winter for Bone and Ramirez (1938) and Herzberg (1938) but in the summer for Dragomiresco (1936) Thompson (1937) found the incidence highest in March and the lowest in July, while Shawan (1938) noted an increase in the spring with a peak in the summer a decrease in the autumn and the lowest incidence in the winter Fallis (1938) had 15 cases in the winter, 25 in the spring 33 in the summer and 27 in the autumn Dineen (1929), Sallick (1936), Heim (1937) and Kelly (1939) considered that there was no significance in the seasonal variations

According to Judin (1940) the second half of winter and early spring have the greatest and July the smallest, number of perforations He suggested that this may be possibly a sequel to the acute infections and lack of vitamins which are prevalent during the winter months

De Bakey (1940) in a collected series of 2 334 cases in which seasonal incidence was mentioned found that 28 6 per cent occurred in the spring 22 4 per cent in the summer 23 9 per cent in the autumn and 25 per cent in the winter In his own series (Odom and De Bakey 1940) the figures were 24 6 24 2 27 9 and 23 2 per cent respectively Kapsinow (1942) reported the highest number of cases for May the lowest seasonal period was the

Dunbar (1926) had 71 2 per cent of 387 cases which occurred during these periods Bager (1929) found that the maximum frequency in 1,767 cases occurred at the age of about 30 years for men and 45 years for women The increase in recent years affected particularly men between the ages of 20 and 40 years This was also confirmed by Semb (1930) James and Matheson (1934) had half of their cases in the fifth and sixth decades Shawan (1938) in 227 cases had the majority occurring in the middle years with a sharp drop over fifty In Judin's (1939) series of 912 cases, 75 per cent occurred between the ages of 20 and 40 years Fallis (1938) reported on 100 patients, the youngest was 18 and the oldest 67 De Bakey (1940) has pointed out that the age incidence in acute perforated ulcer is approximately the same as that of peptic ulcer in general, that is, it occurs with the greatest frequency during adult life in the third, fourth and fifth decades In a collected series of 6,875 cases, 73 1 per cent occurred in patients aged 20–50, 4 per cent before the age of 20, and 22 per cent after 50 years Odom and De Bakey (1940) have reported 78 2, 3 7 and 18 3 per cent respectively for similar age groups In 89 patients seen by McCabe and Mersheimer (1943) the youngest was 21 and the oldest 77 years Estes and Bennett (1944) in 88 cases had 1 (1 2 per cent) aged 10–19, 15 (18 7 per cent) between 20 and 29, 13 (16 2 per cent) between 30 and 39, 23 (28 7 per cent) between 40 and 49, 18 (22 5 per cent) between 50 and 59, 9 (11 2 per cent) between 60 and 69, and 1 (1 2 per cent) between 70 and 79 Black and Blackford (1945) in 90 cases had 8 8 per cent of patients less than 30 years old, 28 per cent less than 40 and 17 were 60 or more years old Baritell (1947) in 88 patients had 12 (13 6 per cent) between the ages of 20 and 29, 23 (26 1 per cent) between 30 and 39, 26 (29 5 per cent) between 40 and 49, 19 (21 6 per cent) between 50 and 59, 7 (8 0 per cent) between 60 and 69 and 1 patient (1 1 per cent) between 70 and 79 Moore and Hendricks (1948) in 101 patients, had 3 from 10 to 20 years old, 13 from 21 to 30, 21 from 31 to 40, 27 from 41 to 50, 28, from 51 to 60, 8 from 61 to 70, and 1 between 71 and 80 Turner (1951) in 224 cases found that the greatest number occurred during the fourth and fifth decades

INCIDENCE IN THE OLD

Perforation from peptic ulcer in the old occurs rarely In his collected series of 6 875 cases De Bakey (1940) had 15 per cent for the age period 50–59 years but only 5 8 per cent for 60–69 years and 1 6 per cent beyond this age Moynihan (1901) reported perforation in a woman of 77 years, Dunbar (1926) in one of 74, and Montgomery (1930) in one of 75 Gilmour and Saint (1932–33) followed up for from 2 to 5 years 64 cases of perforated ulcer The oldest male was 67 and the oldest female 69, the youngest male was 17 and the youngest female was 28 James and Matheson (1934) had a case of 74, their youngest was a male of 19 Sandell (1936) in a review of 5,470 cases had one aged 82 years McCreery (1938) in 170 cases had two cases between 71 and 80 years and one of 81

Meyer and Saphir (1943) suggest that, while it is generally accepted that

following symptoms, (2) those taking place without any previous illness, and (3) those occurring in the course of febrile disease without symptoms of the gastro-intestinal tract

According to Broadbent (1897) premonitory symptoms are as a rule scanty, and this was the general observation at the time Deaver and Pfeiffer (1921) had 20 per cent of their cases which were symptomless, Gibson (1921) 25 per cent, Brenner (1922) 13 per cent in 15 cases, Sherren (1924) 3 per cent in 218 cases, and Meyer and Brams (1926) 31 per cent in 19 cases Mondor and Lauret (1923) observed an exacerbation of symptoms a few days before the perforation Radoievitch (1925) had 21 per cent of his cases symptomless and in another 10 per cent symptoms were noticed for only a few days or weeks In Bager s (1929) review of 1 188 cases of perforation strict interrogation elicited that 127 cases had no symptoms (11 per cent of all cases), 80 had symptoms up to one week 107 up to one month, 175 up to one year, 497 one or more years and 202 intermittently for several years, in 25 per cent of all cases symptoms had not lasted for more than one month In his own cases with a history of more than one month, only 7 per cent had acute pains which lasted a few hours or a few days In some cases the pains were accompanied by a feeling of malaise, rigors and obstinate constipation Blackford and Baker (1931) thought it a striking point in the clinical histories that only 6 of 18 patients had stomach trouble immediately previous to perforation Twelve were relatively or absolutely symptom free at the time of perforation The catastrophe came without warning and without previous clinical diagnosis of ulcer

Gilmour and Saint (1932–33) stated that in 88 per cent of cases the length of the history extended over years and they thought that this had a definite bearing on the perforation and incidence of peptic ulcer, and that the older the ulcer becomes the more likely it is to perforate Thompson (1937) observed that his cases had less than one month s history Shawan (1938) had 82 per cent with a positive history but 14 per cent denied any type of gastric distress Fallis (1938) reported no ulcer history in 11 and a 1–6 month s history in 18 out of 100 patients Blackford and Cole (1939) observed 55 perforations during quiescent periods and 27 during periods of ulcer symptoms

McCreery (1938) thought that the medical history was of little importance Out of 170 cases he had 109 (64 per cent) with a history of one month to 18 years 30 (17 6 per cent) with an indefinite history of 2 weeks to 10 years and 31 (18 2 per cent) with no previous digestive symptoms perforation being the first evidence of disease

De Bakey (1940) found in 211 cases that in 29 (13 6 per cent) perforation was the first manifestation of the disease In the series which he reviewed 15 per cent were free of symptoms Berson (1942) found that of 154 consecutive cases in a total admission of 132 medical and 115 surgical 24 (5 6 per cent) gave no previous history of ulcer The others had symptoms from a few weeks to 25 years—only 8 had radiological evidence of ulcer Kapsinow (1942) reported 8 of 9 patients in whom no history of previous gastric

summer Illingworth, Scott and Jamieson (1944) found the incidence of perforation unduly common in December and relatively uncommon in August, September and October Olson and Norgore (1946) considered that the seasonal incidence was not significant

Estes and Bennett (1944), in a series of 80 cases, noted that 27 5 per cent occurred in the spring, 27 5 per cent in the summer, 22 5 per cent in the autumn and 22 5 per cent in the winter

Jamieson (1947) reviewed the admissions into hospital of 7,829 cases of perforation during the period 1924–1925 Perforations were relatively uncommon in August, September and October and unduly common in December Moore and Hendricks (1948) observed perforations in 23 patients in the autumn, 33 in the winter, 25 in the spring and 20 in the summer In Sure's (1949) series, there were more cases during spring and fewer during winter Turner (1951) in an analysis of 224 cases reported the smallest incidence for April and July and the greatest for October and January

Daily incidence

Judin (1937) stated that perforations rarely happen at night, after break fast the number increases rapidly A second and bigger wave of perforations occurs in the hours after the main midday meal and decreases towards evening, then increases again after supper Illingworth, Scott and Jamieson (1944) found perforations less frequent on Sundays and Mondays and unduly common between the hours of 3–6 p m Chang (1937) found the highest incidence during the afternoon and in the morning, at least two hours after a meal

Meyer and Brams (1926) reported that perforation occurred whilst the patient was sleeping in 5 (8 per cent) of their 62 cases In Bager's (1929) collected series 25 patients had perforation whilst they were undergoing treatment for chronic ulcer in hospital Eliason and Ebeling (1934) had 20 cases of perforation out of 60 patients confined to bed

Thompson (1937) had 20 9 per cent and Fallis (1938) in 74 recorded cases 20 (27 per cent) who were resting at home 7 (9 5 per cent) were in bed at home and 6 (8 1 per cent) were in bed in hospital Judin (1939) had 23 5 per cent in bed in 272 cases

De Bakey (1940) refers to Dowdle (1935) who reported a case in which a second ulcer perforated 6 days following the rupture and repair of the first Odom and De Bakey (1940) had 3 cases which perforated whilst they were in hospital on the Sippy treatment

Moore and Hendricks (1948) found that 14 out of 101 patients perforated after eating or drinking, 27 while in bed of the latter 8 perforations occurred whilst the patients were in a hospital being treated for symptoms of ulcer Luer (1949) in 362 cases had 65 (30 4 per cent) which perforated whilst lying in bed and 35 (16 4 per cent) whilst sitting in a chair—60 occurred on an empty stomach and 45 soon after a meal

Duration of symptoms prior to perforation

Abercrombie (1824) drew attention to three types of perforation (1) those

two or more ulcers not related to each other become perforated, and (3) those in which two perforations occur exactly opposite each other, perforations of the so-called kissing type This they found to be the most common type

Ehrlich (1928) reported a case of a boy of 16, with a history of epigastric distress relieved by food and sodium bicarbonate After 3 years when symptoms were aggravated he had a 3 cm linear perforation of a large indurated ulcer of the lesser curvature on the anterior surface of the stomach While on a Sippy diet he perforated again 6 weeks later The perforation was situated in the centre of a hard cartilagenous tumour involving the first part of the duodenum Repair and gastro-enterostomy were performed Five years later, after 3 weeks of pain he suffered a perforation from a jejunal ulcer situated one inch distal to the gastro-enterostomy

Bager (1929) collected 24 multiple perforations Pearse (1932) in a review of the literature found 33 instances of re perforation in 4 813 cases a percentage of 0 69 Graves (1933) concluded from a survey of 4 402 cases of perforated ulcers in Germany, including 144 personally collected cases, that peptic ulcers are multiple in about 30 per cent of all patients who have perforations and that gastritis atrophic, hypertrophic or ulcerative, is usually present in the ulcer bearing area of the stomach

Brenner (1935) who followed up 24 of 41 patients for 1–20 years observed 18 who were treated by simple closure, of whom 14 (78 per cent) remained symptom free

Lysaght and Williams (1937) reported a patient aged 26 (whose father died at the age of 34 of a perforated ulcer) who perforated 4 times the first perforation occurred in February 1932 and the second in September 1932 in December 1934 a posterior gastro-enterostomy was performed which did not relieve the symptoms Further perforations occurred in July 1935 and August 1936, all in the anterior wall of the pylorus

Gosset Jouanneau and Allamand (1938), reviewing 66 collected cases, added 2 of their own and concluded that a repair operation and gastro jejunostomy in no way influenced the subsequent development of the gastric lesion or prevented re perforation

Bottin (1939) in 195 cases reported 3 cases (1 54 per cent) who had the second intervention 11, 2 and 9 years later respectively

Judin (1939) held the view that there are cases which show an obvious acute inflammatory reaction of the stomach and duodenum and in the vicinity of the ulcer which perforates there may be numerous other smaller ulcers which also show minute perforations He cites the case amongst others of a man of 60 who 14 days after suture of a perforated duodenal ulcer had a perforated gastric ulcer At autopsy it was found that the duodenal ulcer had healed and that besides the perforated gastric ulcer there were three more ulcers on the lesser curvature

De Bakey (1940) in his collected series found an incidence of 1 1 per cent of re perforations and Cohn (1941) found 1 3 per cent in 300 cases repaired at the San Francisco Hospital from January 1935 to June 1940 Royster

complaint could be elicited Of the 89 patients seen by McCabe and Mersheimer (1943), 34 had a definite history and 29 a suggestive history of ulcer, 24 gave no previous history Estes and Bennett (1944) had 3 patients out of 80 who gave no history of antecedent peptic ulcer symptoms, of the remaining 77 the duration of symptoms ranged from 2 weeks to 40 years Bantell (1947) in 88 patients found that only 57 (64 8 per cent) had a history of symptoms and, in addition, a considerable number of these had been having symptoms only for a short while before their perforation In 101 patients, Moore and Hendricks (1948) found that 23 reported having had no chronic symptoms In Luer s (1949) 362 cases there was no previous history in 14 6 per cent, and in 20 1 per cent the symptoms were atypical Nuboer (1951) reported that histological examination of all cases of perforated ulcer treated by partial gastrectomy showed that he was dealing with a chronic ulcer which had caused considerable changes in the submucosa and deeper layers Forty (1951) found that in his series 75 per cent were acute ulcers and that differences in histological interpretation may account for the difference recorded in previous records

Turner (1951) reported the autopsy of 24 patients who had not had operative intervention 8 of these had a typical ulcer history, 2 had no history, 5 were associated with other major pathology of possible aetiological significance, 9 had no history but some form of sepsis Turner found that in 82 (44 per cent) of 185 patients the acute exacerbation lasted from one day to two weeks, with fatigue, upper respiratory infections, exposure to cold and damp weather, worry and anxiety as contributory factors Out of *185 patients, 15 were without symptoms*

Re-perforation

Brunner (1903) quoted by Hauser (1926) found in 120 autopsies for perforation that there were 39 cases (32 per cent) with several ulcers present which had not perforated

Massie (1924) reported an unusual case of simultaneous perforation of an acute ulcer situated in the afferent loop and a chronic ulcer situated at the anastomosis of an anterior gastro-enterostomy which was performed in a patient with a three year history of chronic indigestion Six months after operation symptoms appeared characteristic of secondary ulceration, obstructing the anastomosis He collected from the literature 36 cases of perforated jejunal ulcer following gastro-jejunostomy and observed that it is *significant that these ulcers which were situated some distance from the* anastomosis, were of the acute type, as in each of the reported cases perforation followed within a few days of the original operation, the shortest being 5 and the longest 14 days Masson and Simon (1927) reviewed the literature of multiple perforated gastric ulcers and could find only 32 authentic cases, they reported one in a boy aged 18 with a perforated ulcer on the anterior wall of the stomach and a second perforated ulcer on the posterior wall almost opposite the other They classify multiple perforations in 3 groups (1) those in which there are multiple perforations in a single ulcer (2) those in which

digestion but rather to infection may be surmized from the parallel phenomenon of perforation of carcinoma of the caecum when hydrochloric acid cannot possibly be involved in the destructive process)

Haemorrhage and perforation in the same subject

The old adage that haemorrhage and perforation exclude each other in the same subject cannot be sustained although their simultaneous occurrence is a rare phenomenon

Mondor and Lauret (1923) had 1 case of haemorrhage in 75 cases of gastric perforation and 4 in 75 cases of duodenal perforation Sherren (1924) had to operate on several patients whose chronic ulcers had perforated, or caused haemorrhage while they were undergoing a course of treatment in bed Bager (1929) in 40 cases out of 1 188 perforations reported haemorrhage with or immediately before or after the perforation Raven (1930) had two cases of melaena and one haematemesis in 80 cases of perforation Finsterer (1931) observed only three times perforation and haemorrhage in the same subject Berg (1931) reported 2 cases which had haemorrhages and perforated while in hospital James and Matheson (1934) had three cases which gave a history of haematemesis in 75 cases of perforation

Both manifestations were observed by Eliason and Ebeling (1934) in 24 out of 240 collected cases of perforation to which they added 9 of another 54 cases of perforation and 9 cases of melaena in 51 cases Goldman (1936) had 6 in 56 cases of perforation Vale and Cameron (1936) found in 7 cases of perforation which occurred while they were undergoing treatment in hospital that 4 had previously had haemorrhage Shawan (1938) had 17 cases of haemorrhage in 227 cases of perforation Harkins (1938) mentions 5 cases of both haemorrhage and perforation in the 94 cases following burns which he investigated in detail McCreery (1938) observed 5 cases of haematemesis and 13 of melaena in 170 cases Judin (1939) saw at least 10 cases which were admitted for profuse haemorrhage and perforated whilst in hospital Winters and Egan (1939) had a 10 per cent incidence of bleeding in 362 cases of perforation In 13 patients who came to autopsy without bleeding 3 had multiple ulcers and of 8 with bleeding 7 had multiple ulcers Bleeding and perforation occurred in 1 per cent of all cases admitted to hospital with peptic ulcer during 1937 and 1938 De Bakey (1940) reviewed 155 cases (6 1 per cent) of haemorrhage in 2 525 cases of perforation

McCabe and Mershеimer (1934) saw 89 cases of perforation 15 per cent with haemorrhage Estes and Bennett (1944) in 80 cases found an association of both conditions present in 26 9 per cent Gordon Taylor (1945) reported that a colleague had a patient in hospital who within a few weeks suffered two haemorrhages and two perforations of a duodenal ulcer The first perforation took place 10 days after the first severe haemorrhage the second haemorrhage occurred 14 days later and during the period of recovery the second perforation took place Olson and Norgore (1946) had 166 cases of acute perforation in 97 per cent of which the onset of epigastric pain was sudden bleeding occurred in 13 per cent Kaye (1946) described a case of a

(1942) reported a gastric ulcer high on the greater curvature of the stomach in a woman aged 23 which perforated 5 times

Berson (1942) in 154 cases of perforation had 3 patients with recurrence One had a gastric ulcer perforation 7 years previous to a perforation at the first portion of the duodenum The second patient had 2 perforations within 4 years and the third 2 within one year

Estes and Bennett (1944) found re perforation in 7 of 61 patients (11 per cent) treated by simple suture, Williams (1944) in 3 of 100 patients, Wakeley (1944) 2 in 100 patients, Baritell (1947) 6 in 88 patients, and Moore and Hendricks (1948) in 5 per cent Mahoney and Sands (1937) reported the case history of a patient who had 3 distinct and separate peptic ulcers which perforated, the first in 1916 aged 29 years, the second in 1932 and the last in 1936 On each occasion simple closure was performed Werbel, Kozoll and Meyer (1947), in 4,355 patients admitted over 7 years (1939–45) for peptic disorders, had readmissions of 11–14 per cent each year Multiple perforations occurred in 42 of these cases (17 per cent), 35 had 2 perforations, 5 had 3 perforations, 1 had 4 and 1 had 5 perforations

Ivy, Grossman and Bachrach (1950) suggest that the lower mortality rate of re perforation which is significantly less than that of perforation (Lysaght and Williams, 1937, De Bakey, 1940) is probably due to immunization by the first perforation

Perforation in carcinoma of the stomach

Chavannaz and Radoievitch (1928) gave details of 47 cases of perforation of gastric carcinoma recorded in the literature They stated that Laennec in 1824 diagnosed a perforation of a carcinoma of the stomach which was con firmed by autopsy They quote Zuccarcelli s case published in a medical journal in Marseilles in 1891 of a man aged 30 with a history of a few months of dyspeptic symptoms, admitted to hospital where he was diagnosed as suffering from gastric cancer His condition deteriorated when he was suddenly taken ill with violent abdominal cramps associated with an eleva tion of temperature and rapid death At autopsy three perforations were found on the anterior surface of the stomach and a large perforation was found on the posterior surface of the stomach Aird (1935) described a case of perforation of a carcinoma of the stomach in a ship s mate aged 27 years and 7 other cases treated at the Royal Infirmary, Edinburgh he also review ed 79 cases from the literature Eusterman and Balfour (1935) observed 3 5 per cent of perforations in their surgically verified cases of gastric carcinoma McNealy and Hedin (1938) reported 133 perforations (4 04 per cent) in 3,289 cases of gastric carcinoma admitted to hospital Doll (1950) reported on 17 instances of perforated carcinoma of the stomach which occurred at the Central Middlesex Hospital during 11 years (1938–48) among 452 patients operated on for perforation of the stomach or duodenum Kennedy (1951) observed that, of a total of 111 acute perforations in 5 years 6 proved to be carcinomatous

(That perforation of carcinoma of the stomach is not due to peptic

and the acute erosions were identical lesions Brenner (1922) found in his two cases with no antecedent history that evidence of inflammation and repair were absent, but one had a perforated appendix and the other a pelvic infection Moutier (1924) believed that an infective factor was involved in the perforation of both the acute and the chronic ulcer In acute ulcer, perforation represents the whole lesion and the complete disease, it is a summary of the life history of the ulcer, but in chronic ulcer it represents only one episode in its development He suggested (Moutier 1926) that the acute infection or the toxic process affects the wall of the viscus produces a complete necrosis and leads to a complete parietal perforation (perforation complète d emblée) Hauser (1926) pointed out that perforation of pinhead sized ulcers can occur from haemorrhagic infarcts before the development of chronic changes Even in large callous ulcers the perforation can be so small that it is difficult to identify He quotes Lohr (1916) who observed 3 cases of perforation in a scar

Cushing (1932) reported three cases of perforation, after operation for cerebellar tumour, causing death respectively in one, two and four days after the surgical intervention All the lesions were acute showing heavy infiltration of polymorphonuclear leucocytes involving all coats even the serosa, unmistakably an ante mortem process There was no evidence of chronic inflammatory reaction These cases showed a sudden and marked rise in temperature

Eusterman and Balfour (1935) pointed out that perforation may occur in any part of the stomach which previously has not been involved with disease They reported the case of a patient from whom they had excised a gastric ulcer on the lesser curvature and performed gastro-enterostomy Death occurred 13 days after this procedure The first week of convalescence was perfectly normal but on the tenth day a sudden attack of abdominal pain occurred, with increased rigidity and shock and all local and general evidence of leakage They give reasons why a secondary procedure was not considered At necropsy an acute *perforated* ulcer on the anterior wall of the stomach, midway between the lesser and greater curvatures was found, the perforation was not much larger than 1 mm in diameter and therefore there was practically no induration about the opening

Newburger (1937) believed that a correlation exists between the length of the ulcer history and the size of the perforation In 9 cases in which these two factors could be estimated accurately 7 with a long history had perforative ostia averaging 13 3 mm in diameter while 2 with perforation without prior history had ostia of 0 5–1 0 mm in diameter

Judin (1939) observed that in cases of perforating ulcer a severe bacterial infection was invariably present The patients had a temperature which was associated with infections such as acute tonsillitis before the ulcer perforated

McCabe and Mersheimer (1943) found in 89 patients who suffered perforation that 8 had an infected appendix

Graham and Tovee (1945) in reviewing a series of 114 patients submitted to operation for perforated ulcer, concluded that in cases without previous

man aged 55 who suffered from a perforation of a prepyloric ulcer which was followed 6 days later by profuse haemorrhage from another ulcer situated on the lesser curvature 7 cm from the oesophageal opening Werbel, Kozoll and Meyer (1947) had 82 (34 per cent) of 239 patients who had previously perforated readmitted for haemorrhage, three patients who died of haemorrhage had a second perforation as well

Avery Jones (1947) had 5 patients with perforation after admission for haemorrhage and there were 14 others who bled after perforation Moore and Hendricks (1948) in 101 cases of perforation had 20 per cent with haemorrhage In Luer s (1949) 362 cases, 24 6 per cent had perforation plus haematemesis or melaena Luer (1950) followed up 102 cases of perforated ulcer over an average period of five years, 21 6 per cent remained asymptomatic, 33 3 per cent had haemorrhage (6 9 per cent massively) and 10 8 per cent had another perforation Cates (1950) had 9 per cent in 41 cases and Turner (1951) 5 3 per cent in 209 cases Slater (1951) described 3 cases which bled and perforated simultaneously

Experimentally, Burdenko and *Mogilnitzki (1926) produced concurrent* haemorrhage and perforation by stimulating the brain in dogs

It may be reasonably concluded that both haemorrhage and perforation, which are manifestations of the acute ulcer, are produced by an indentical causative agent

Infection and perforation

Billroth (1867) pointed out the connection between perforation of ulcer and conditions of general septicaemia and the occurrence of perforation as a complication following burns

Korte (1875) stated that micro organisms can be identified in the lesion only if the ulcer perforates

Fenwick (1892–93) reported that in the records of the London Hospital (during the previous 30 years) there are numerous examples of acute gastric ulcer exhibiting a tendency to rapid perforation In some instances the disease complicated certain specific fevers, such as typhoid and erysipelas, in others the ulceration appeared to be the direct result of pyaemia whilst in several instances it was associated with severe burns of the skin, duodenal ulceration also being present In all cases, where death had occurred from the primary disorder, the ulcers were multiple

Dudgeon and Sargent (1905), who made a bacteriological study of peritonitis, reported 4 perforated duodenal ulcers, 3 sterile and 1 infected with *B coli* and 9 perforated gastric ulcers all infected with *Staphylococcus albus* Dieulafoy (1905–6) described cases of perforating ulcer of the duodenum and perforating ulcer of the stomach consequent to acute infection of the appendix Hayem (1911) stated that these perforations are encountered almost exclusively in association with a septicaemia or gangrenous condition as well as with burns, he drew attention to the fact that when additional lesions are present after perforation following burns these are always mucosal erosions, and he deduced from this observation that the ulcer which has perforated

(1928–29) post mortem examinations of 1,323 children up to thirteen years old 70 per cent were in the first year of life In 56 there were haemorrhagic erosions Of the 19 cases with ulcer six had tuberculous meningitis or syphilis Usually, the lesions were found accidentally at necropsy Somerford (1930) reported a case of a duodenal perforation in an infant aged 14 days Brockington and Lightwood (1932) reported one case of a wasted infant with a perforation of the second part of the duodenum at the age of ten weeks and another, aged two weeks, born at term with a body of a premature infant with a perforation at the junction of the first and second parts of the duodenum Dunham (1933) found three cases of gastric ulcer in 20 post mortem examinations following septicaemia in the newborn Dunham and Goldstein (1934) reported 2 cases of rupture of the stomach in which *B coli* was found in blood cultures Seinsheimer (1935) observed, in an infant aged four days, a small perforation in the second part of the duodenum which showed no cellular evidence of inflammation Thelander and Mathes (1939) diagnosed roentgenologically a perforation of the duodenum in a one-day old infant that died 10 days later with sepsis The ulcer was 2 cm below the pylorus and measured 1 5 x 0 8 cm

Thelander (1939) compiled 85 reported cases of spontaneous perforation in infants, there were 16 instances of perforation of the stomach 30 of the duodenum and 39 of the remaining portion of the gastro-intestinal tract. Bird Limper and Mayer (1941) reported a case of perforated duodenal ulcer sutured 34½ hours after birth, with recovery At laparotomy the perforation was found on the anterior superior surface

Schlumberger (1951) observed in a series of 251 consecutive autopsies on infants and children 1 case of multiple acute gastric ulcer, 2 cases of gastromalacia and 7 of acute duodenal ulcer which were all associated with cerebral damage (meningo-encephalitis in 3, bulbar poliomyelitis in 2, oedema and anoxia in 2 and intraventricular haemorrhage sinus thrombosis and microcephaly in 1 each)

Kennedy (1933) stated that ulcers in children appear to fall into several distinct groups according to the age of the patient (1) the ulcer of the newly born which makes its presence known by melaena neonatorum This lesion is an acute one which either heals rapidly or else causes death of the infant by haemorrhage or peritonitis (2) the ulcer which occurs in children from a few weeks of age to about the end of the first year of life These lesions are also acute and epidemic infections may be concerned in their aetiology, (3) the ulcer found in children aged 1–9 years These lesions are chronic, in the sense that they may be present for a long time

Prenatal perforation of the appendix has been described by Jackson in 1904 Hill and Mason in 1925 and Abt in 1931 (Thelander, 1939)

Conclusions

It is generally agreed that the acute ulcer perforates without premonitory symptoms and without any antecedent history of dyspepsia (perforation complète d'emblée) When an inactive that is to say, symptom free, chronic

history the perforation was due to an acute ulcer "possibly metastatic from remote infection"

Korttila (1951) in his detailed investigation of 38 cases of perforation (34 males and 4 females) with an average age of 43 (20-72), gives the temperature on admission to hospital as below normal (shock) in 47 per cent and above normal in 53 per cent Leucocytosis was more common in the early than in the late cases On admission the gastric contents were anacid in 18 of 38 cases and hyperacid in 3 The amount of hydrochloric acid was smaller in 78 per cent in the perforation phase than in the recovery phase Increased or normal values obtained 9–10 days after operation in patients with anacid or subacid values in the perforation phase

Perforation in infants

Perforation in infants is of special significance although it may be said that on the whole acute perforated ulcer in infants occurs rarely It affects exclusively the obviously undernourished and grossly debilitated child The lesion is invariably an acute ulcer

Finny (1908–9) described as particularly interesting a case of an infant, normal at birth, developing pyloric stenosis, with several attacks of melaena followed by perforation at the age of $2^1/_2$ months One of the two duodenal ulcers, $1^1/_2$ inches from the pylorus had perforated but both had a clean, punched out appearance and there was considerable inflammation of the duodenum The pyloric opening was very narrow, the mucous membrane appeared healthy but the muscular coats were firmer and thicker than usual A small quantity of bile coloured fluid was seen oozing from the perforation the child having had a considerable amount of bile in the stools from birth The edge of the perforated ulcer showed inflammatory round cell infiltration

Helmholz (1909) stressed the relationship of peptic ulcer with perforation in marasmic or athreptic infants

Schmidt (1913) observed 20 cases in 7 years a proportion of 1 8 per cent in 1,109 post mortem examinations The age was 5 days to 11 months Several had multiple perforations Holt (1913) found that the age incidence is striking and that it corresponds very closely with the age incidence of deaths from marasmus In 65 cases 9 occurred in the newborn, and 70 per cent from the sixth week to the fifth month, the greatest frequency between the sixth and tenth weeks

Gerdine and Helmholz (1915) drew attention to the epidemic character of the disease Paterson (1922) pointed out that its occurrence is more frequent in marasmic children and it may be present in melaena neonatorum

In a series of 248 cases of ulcer of the stomach and duodenum in children, reported by Theile (1926) 138 occurred in the first year and of these 83 or one third of the entire series were found in the first month of life In 95 cases the ulcers were multiple Butka (1927) reported a case in an infant which vomited on its third day when the temperature rose to 102 6° F , haemorrhage occurred on the fourth day and perforation on the fifth In Berglund s

cancerous diathesis Rokitansky (1842) thought that cancer occurred some times in simple ulcer and that it might arise from the ulcer, while Dittrich (1848) in 160 cases of cancer of the stomach found 6 developing near the ulcer, in 2 of these the carcinoma being limited by the edge of the ulcer Steiner (1868) and Wollmann (1868) estimated at 4 per cent the proportion of carcinoma arising in ulcer (Newcomb 1932)

Brinton (1857) emphasized the desirability of discriminating between the cancerous degeneration of the hard margin of an ulcer and the ulceration of a growth originally cancerous , as he believed that it was possible for a new growth to become secondarily ulcerated in such a manner as to destroy cancer cells and leave only an apparently benign peptic ulcer in its place

The view that ulcer may become cancer was supported by Zenker (1882) Dieulafoy (1897), Mathieu (1898), Hayem (1911) Balfour (1919), Moynihan (1923) Finsterer (1927) *Stout* (1932) *Hurst* (1935) *Guttman Bertrand* and Peristiany (1939), Ransom (1947) and Jordan (1948), but was refuted by Duplant (1898) Schmidt (1910) Holland (1914), Ewing (1918, 1936) Nielsen (1919), Stewart (1923), Morley (1923), Aschoff (1924), Dible (1925 1937) Lameris (1925), Orator (1925), Cabot and Adie (1925), Patterson (1926) Hauser (1926), Bevan (1927) Walton (1930), Brown (1930), Mattison (1931) Newcomb (1932), Barclay (1933) Konjetzny (1934) Sauer (1935), Chang (1936) Hinton and Trubek (1937) Bockus (1943), Templeton (1944) Heuer (1944) Levin Kirsner and Palmer (1949a) Shay and Lorber (1951), Swynnerton and Truelove (1951)

Luff (1929) found that in 406 cases operated on for gastric ulcer not a single case of carcinoma developed after 4–9 years

Pathological observations

The difficulty of the histological diagnosis of the specimen is shown by the *numerous contradictory observations based on different standards of* interpretation MacCarty s (1910) observations which are now obsolete of the carcinomatous transformation of 71 per cent of gastric ulcers (Wilson and MacCarty 1909 Wilson and McDowell 1914) have been refuted by Newcomb (1932) and Konjetzny (1934) Walters Gray and Priestley (1941) stated that in the experience of the Mayo Clinic in 10 per cent of the cases no distinction can be made between benign and malignant gastric ulcer by roentgenological methods and surgeons have called attention to the fact that a definite proportion of the patients operated upon for cancer of the stomach had been reported by the roentgenologists to have gastric ulcer (also 10 per cent)

Vines (1940) *has pointed out that the mucous membrane* at the edges of a chronic simple ulcer generally shows a well marked reparative hyperplasia which may exhibit hyperchromasia of the nuclei and even cells *in mitosis* It is thus easy to mistake such changes for early malignancy and it is sometimes very difficult to determine which of these two changes is present

Ivy Grossman and Bachrach (1950) concluded from a review of the subject that development of cancer from benign ulcer of the stomach is a very

ulcer perforates, careful investigation will disclose a sudden exacerbation of *the pain which is extremely short in duration and which coincides either with* an acute attack of fever, such as a common cold or "influenza", or with sudden trauma produced by unusual strain (coughing and sneezing) Chronic lesions as such are not apt to perforate as they tend to produce generalized inflammatory reactions and fibrosis, and become adherent to neighbouring structures, the danger and the extent of the perforations being thus minimized and limited No doubt, in a long standing penetrating ulcer, the active process can continue for a sufficiently long time to lead to perforation into the adherent structure, or penetrate a blood vessel to produce massive haemorrhage Since the perforation constitutes the acute process and an acute ulcer can perforate into a part of the stomach which previously has not been involved in disease (Eusterman and Balfour, 1935) there appears to be no valid reason why it should not also perforate in some diseased part of the organ so that the chronic lesion is subject both to acute and chronic perforation Indeed, Silverman (1947) reported an acute perforation of a chronic ulcer in a man aged 45 years, who suffered from gastric trouble for some years, not serious enough to interfere with his work, with epigastric pain one hour after food which lasted only half an hour and was relieved by alkaline powder Radiological examination showed an ulcer of the lesser curvature The patient died suddenly from perforation of the ulcer, necropsy disclosing no food, blood or fluid in the peritoneal cavity

The apparent paradox, that when chronic ulcer and acute ulcer are encountered simultaneously the presence of the former antedates the latter is thus easily explained

It is of practical interest to recall that Mayo (1908) quoting the French aphorism ulcère perforé ulcère mort—(perforated ulcer, dead ulcer) recommended simple closure, and that Boles (1948) and Mayo and Fitchett (1950) who reviewed the operative mortality rate of patients with perforated gastric and duodenal ulcers concluded that simple closure of the perforation is the treatment of choice Taylor and Warren (1956) advocate aspiration in all cases of acute ulcer

MALIGNANT TRANSFORMATION OF PEPTIC ULCER

Incidence of ulcer—cancer

Apart from the theoretical interest of the malignant transformation of chronic peptic ulcer this aspect of the problem has obviously considerable practical importance and it is essential to establish, if possible, in what proportion, if at all peptic ulcer becomes malignant The problem is restricted to gastric ulcer because primary carcinoma of the first part of the duodenum is practically unknown The differentiation of gastric and duodenal ulcer in their relation to malignant transformation assumes therefore a fundamental significance

According to Cruveilhier *(1839) this question* could be answered in the affirmative only for those individuals who were already affected by the

the lesion tends to increase the secretion of hydrochloric acid, on the other hand, carcinoma is invariably associated with an atrophic mucous membrane which may ultimately lead to a complete cessation of acid secretions The simultaneous presence of benign ulcer and independent carcinoma points to the simultaneous presence of two unrelated morbid processes

Whilst it need not be argued that both carcinoma and ulcer may be produced by some form of irritation which, admittedly, is of a different nature, *the consequences are fundamentally different in as much as*, in the former, there is stimulation of the tissues which leads to unrestrained proliferation, and in the latter there is erosion which produces the destruction of the tissues — two diametrically opposed morbid processes

unusual occurrence, that if a gastric ulcer is found to be malignant it must have been malignant at its inception

According to Shay and Lorber (1951) unequivocal proof that a gastric ulcer may undergo malignant degeneration is difficult to find They fully subscribe to the opinion expressed by Bockus (1943) that carcinoma of the stomach and peptic ulcer are distinct diseases and that cancer does not occur any more often as a graft upon a gastric ulcer than should be anticipated, considering the high incidence of gastric carcinoma in the population as a whole

Hydrochloric acid level of the gastric content

There appears to be an intimate but inverse relationship between gastric cancer and the acid level of the gastric contents, that is to say, as the carcinomatous tumour progresses so the acid secretions tend to regress

Ulcer and cancer in the same stomach

According to Stewart (1931) it is a rare event for a simple chronic ulcer and a carcinoma to occur independently in the same stomach In a series of 366 operation specimens examined (1921–1931) there were but 3 instances and in a still larger series in the post mortem room the incidence was even less In only 1 case, seen at autopsy, were the 2 lesions situated side by side Their independence was manifest, since they had obviously come together in consequence of the spread of the carcinoma Wilbur and Rivers (1932) reported 33 cases of associated cancer of the stomach and duodenal ulcer which had been encountered at that time at the Mayo Clinic, 19 had active duodenal ulcer 6 had perforating and 7 had healed duodenal ulcers Konjetzny (1934) quoted the observations of Anschutz and Wanke who found in 4 cases which had been operated on for ulcer (gastro-enterostomy) that subsequently carcinoma developed in a different situation from where the ulcer had been Bockus (1943) and Yarnis (1947) have reported cases of benign ulcer and independent carcinoma in the same stomach Pillmore (1946) has shown radiologically the simultaneous occurrence of a benign chronic ulcer on the lesser curvature of the stomach which had perforated and an annular defect of the pylorus due to carcinoma According to Magovern, Friedman and Freund (1953) 98 cases of coexistence of duodenal and gastric carcinoma have been reported in the literature in the last 30 years Stewart (1955) found in 1,503 stomachs, the independent coexistence of 13 cases of gastric ulcer and cancer

Conclusions

In considering the problem of the malignant transformation of the benign lesion certain fundamental differences must be taken into consideration It is generally recognised that the chronic ulcer persists only in an acid milieu with an active mucous membrane which is continually secreting, however long standing may be the activity of the ulcerative process, the persistence of

the sympathetic. Morley (1931) believed that the vagi may take a share in the transmission of visceral pain impulses

According to Heinbecker and O Leary (1933), the vagus below the dia phragm is almost a purely motor nerve Harper, McSwiney and Suffolk (1935) identified two groups of afferent fibres in the abdominal vagus nerves of the cat. According to Davis and Pollock (1936) it is only the efferent fibres of the autonomic system which are concerned with the production of pain and that such afferent fibres as travel along with it belong to the ordinary spinal sensory system

Bentley and Smithwick (1940) who performed unilateral splanchnicectomy and lumbar sympathectomy in patients with essential hypertension found that pain is felt only on the non-operated side of the abdomen After bilateral splanchnicectomy and lumbar sympathectomy no pain is experienced.

Similar observations were made by Balchum and Weaver (1943) Ray and Neill (1947), and Bingham, Ingelfinger and Smithwick (1950)

Ray and Neill (1947) corroborated the observations of Wolf and Wolff (1943) in respect of the appreciation of temperatures and also showed that temperature sense (always closely allied with pain sense) is eliminated from the stomach by interruption of the sympathetics The ventral parietal peritoneum retained its normal sensitivity after double sympathectomy and must be supplied, therefore by somatic afferent nerves while the dorsal peritoneum which possessed Pacinian corpuscles loses its pain sensitivity after bilateral sympathectomy

According to Bentley (1948a) the fibres which conduct pain impulses rom the abdominal viscera are similar to somatic afferent fibres in that they are myelinated and have their cell stations in the posterior root ganglia They run in the splanchnic nerves passing without interruption through the sympathetic ganglia to reach the cord

Ruch (1949) stated that the afferent limbs of the reflex arc which carry out the reflex control of vital visceral phenomena are without exception found in parasympathetic nerves and the afferent fibres of the sympathetic nervous system are not essential to the reflex regulation of the viscera lorgans

SENSITIVITY OF THE ABDOMINAL VISCERA

Lennander (1903) showed, under local anaesthesia of the abdominal wall the insensibility to cutting pricking or burning of the serous muscular and mucous coats of the whole gastro-intestinal tract above the anus

Mackenzie (1909) believed that pain may be derived (1) directly from the viscus—splanchnic pain, and (2) indirectly from the viscus—somatic pain He explained (Mackenzie 1920) all visceral pain as referred by a system of 'reflexes' through the splanchnic afferent nerves to the cerebrospinal nerves of the abdominal parietes and postulated a viscero-sensory reflex and a viscero-motor reflex.

Meyer (1920), Breslauer (1921) and Kappis (1925) suggested that pain arose from the mesentery Tyrell Gray (1922) advanced the view that the Pacinian corpuscles in the mesentery conveyed the impulses Ryle (1926) and

CHAPTER 7

PAIN IN RELATION TO THE PEPTIC ULCER PROBLEM

The pain pathway from an abdominal organ may be traced as follows The axons of free nerve endings in the walls of a viscus follow the artery of the abdominal aorta where they traverse the collateral ganglia without synapse and enter the splanchnic nerve to join the ganglion of the sympathetic chain which is traversed, without synapse, to reach the spinal nerve closest to the spinal ganglia The cell body of the viscero-sensory fibre is situated in the sensory ganglion and the central process enters the spinal cord by the dorsal root, where it connects with somatic motor neurones, with pre ganglionic fibres and with the neurones of the spino thalamic tract (Ruch, 1949)

The reflex arc which controls the visceral organs is composed of 3 neurones

(1) The nerve fibres which conduct impulses from the viscera and their cell bodies which are located in the posterior root ganglia or their cranial equivalent contribute the *afferent* neurone They enter the spinal cord in association with the somatic afferent fibres of the same nerves
(2) The *connector* cells leave the spinal cord to join the peripheral ganglia and represent the *pre ganglionic*, medullated (white) neurone
(3) The *excitor* cells leave the peripheral ganglion to join the viscus and represent the *post ganglionic* non medullated (grey) neurone
The pre ganglionic and the post ganglionic fibres constitute the efferent neurone

Intra abdominal sensation is represented in a cortical area at the lower end of the precentral gyrus (Rasmussen and Penfield, 1947), pain impulses from the stomach which are carried by the splanchnic nerves, can ascend as high as the cerebral cortex (Downman, 1951)

THE ROLE OF THE VAGUS AND SYMPATHETIC NERVES

Pi Sunner and Puche (1925) considered the splanchnics as the true sensory nerves and the vagi as regulating the conductivity of the splanchnics McCrea (1926) stated that the vagi are both efferent and afferent, transmitting centrifugal and centripetal impulses and are concerned with the motor, vasomotor, secretory and sensory functions of the stomach

Kinsella (1929) suggested that clinically there may be two components of abdominal pain and that they are probably subserved by different nervous connections, the truly visceral pain by the vagus and the referred pain by

Site of ulcer pain

Many contradictory theories have been advanced to explain the site of ulcer pain

Hurst (Hurst and Stewart, 1929) claimed that in peptic ulcer, the area of deep tenderness observed by palpation under the x ray screen corresponds to the ulcer crater and is evidence that the subserous layer of the visceral peritoneum is sensitive to pressure Morley and Twining (1930–31) found that the area of deep tenderness on the anterior abdominal wall corresponded generally with the ulcer crater and shifted in position with the ulcer According to Palmer and Heinz (1934) ulcer pain arises at the site of the lesion Leriche (1939) thought that the patient is vaguely aware of the site of pain in visceral organs and particularly when he is a trained observer like a medical man he can distinguish the pain of one visceral organ from another Kinsella (1939) believes that the peculiarities of the pain and tenderness of peptic ulcer cannot be accounted for unless the sensitivity of the actual lesion is admitted

Epigastric pain in hypochlorhydric patients is produced by the ptosed stomach dragging on the gastrohepatic ligament and is situated in the lesser omentum and not in the body of the stomach

PAIN PRODUCING FACTORS IN PEPTIC ULCER

The production of pain in ulcer cases is initiated by the action of an adequate stimulus it may be related to the presence of the inflammatory process the effects of hydrochloric acid on the gastric mucous membrane and the mechanical effects induced by tension of the muscular wall

Adequate stimuli

It is evident that an adequate stimulus is necessary for the production of a painful reaction Adequate stimulus according to Sherrington (1906) means that adaptation has evolved a mechanism for which one kind of stimulus is appropriate Given a sensitive lesion the production of pain depends on the presence of an adequate stimulus It has been shown that this may be either mechanical or chemical

Stimulation of the parietal pleuro peritoneum by scratching or rubbing results in sensations of pain, whereas stimulation of the visceral pleuro-peritoneum is painless Traction on the mesentery and distension of a hollow viscus are adequate stimuli for the production of pain which is caused by stretching of sensory nerves while spasm of the gastro intestinal musculature and increased tension of the musculature of a distended viscus are adequate stimuli for the production of pain

Inflammation

Lennander (1902) noted that the inflamed walls of the stomach and intestine were quite insensitive to mechanical stimuli This observation was confirmed by Morley (1931) Tinel (1937) suggested that the pain of inflamed viscera is brought about by spasm or tension, and Palmer (1943b) that the inflammation lowers the pain threshold

Payne and Poulton (1927) suggested that tension of the muscular coats produced pain in the viscus, the stretching producing deformity of the nerve endings Morley (1931) observed the acute sensibility of the parietal peritoneum and the insensibility of the visceral peritoneum Ray and Neill (1947) believed that pain sensitivity was situated at the mesenteric visceral angle According to Downman, McSwiney and Vass (1948) the intestine has a sensory nerve supply which is anatomically and physiologically distinct from that of the adjacent mesentery According to Bentley (1948a) pain arises directly from the viscus

Referred pain

Penfield (1925) suggested that impulses arising from a viscus may produce referred pain by means of an axon reflex in the sympathetic nervous system which leads to angiospasm or other changes in the periphery, and that these changes in turn produce pain impulses which thus have their origin in the area of reference Infiltration of the skin over the painful area with novocain causes abolition or diminution of the pain (Weiss and Davis, 1928) Leriche (1939) believed in an intrinsic visceral sensibility and he rejected the conception of referred pain Lewis and Kellgren (1939) believed that there was no special form of pain and no viscero sensory or viscero motor reflex Ruch (1947) accounts for most of the phenomena of referred pain on the basis of the convergence of visceral and cutaneous afferents on the same spinothalamic tract neurones

According to Cohen (1947) interruption of nerve paths between the periphery and the central nervous system in those somatic segments which are homologous with those of the diseased viscus abolishes or diminishes the pain or modifies the time of its appearance There is a constant stream of subliminal pain impulses passing to the central nervous system from terminals both in the viscera and the periphery Harman (1948) suggested that the pain is not felt in any particular structure in the body such as viscera or body wall but *that it is best regarded as a projection from the brain* According to Kellgren (1949) the false localisation of the deep pain associated with phantom tumours (Cohen, 1947) results from a central misinterpretation of its source

Sensitivity of the normal stomach

The sensitivity of the normal stomach to an adequate stimulus is proved by the "hunger pang , while the sensitivity of the diseased stomach is proved by the existence of "ulcer pain" (Cannon and Washburn, 1912) Once innervation is established, future migration of an organ makes no difference to localization of pain (Brown, 1948, 1949 Poulton, 1949) There appears to be no explanation why digestive contractions should be painless when hunger contractions are not

Certain forms of gastric stimulation give rise to painful sensations, strong chemical stimulation of the gastric mucosa always gives rise to pain In certain types of gastritis substances normal for the stomach cavity, for example water or gastric juice, may cause pain Strong tonic contractions of the stomach also give rise to pain

(1925), Smith and Paul (1931), Christensen (1931), Bloomfield and Pollard (1931), Kellogg (1933), Balchum and Weaver (1943), Jones (1943), Kuntz (1946) and Hightower and Gambill (1953) but Ortmayer (1925), Cobet and Gutzeit (1926), Berg (1926), Gutzeit (1929), Hess and Faltitscheck (1928), Palmer and Heinz (1934) were unable roentgenologically to correlate ulcer pain with spastic and peristaltic changes in the stomach McDowall (1934) pointed out that it is quite unphysiological to have prolonged pain caused by peristalsis, for the pain, if severe enough causes sympathetic stimulation and paralyses the gut

Hunger contractions

Dundon (1917) observed that the tracings obtained from the empty or nearly empty stomach of ulcer patients at the time when ulcer pains are felt do not reveal contractions appreciably stronger than those of the empty stomach of the average normal person, an observation which was confirmed by Carlson (1917) Palmer (1927) pointed out that the pain of ulcer normally disappears on starvation Patterson and Sandweiss (1942) recorded ulcer distress when the duodenum was in an active state of motility regardless of the state of the gastric phase

BEHAVIOUR OF THE PYLORIC SPHINCTER DURING GASTRIC PAIN

The significance of muscular tension and the peristaltic wave in its relation to ulcer pain cannot be fully appreciated without taking into account the behaviour of the pyloric sphincter during gastric pain

Hurst (1911) believed that the pain was due to acid stimulation of gastric peristalsis which produced inhibition of pyloric relaxation

Enriquez Binet and Durand (1914) demonstrated roentgenologically that the occurrence of hunger pain—the douleur tardive—always corresponds with the momentary arrest of gastric evacuation They quote Meunier who found that if milk was given during an attack of hunger pain it did not begin to leave the stomach until the moment the pain disappeared Hurst (1922) observed that the relief of pain produced by bicarbonate of soda occurred at the moment when the carbon dioxide was evacuated by belching the raised intragastric pressure forcing some of the gastric content through the pyloric canal Kinsella (1928) observed roentgenologically immediate relaxation of the pyloric sphincter after the administration of bicarbonate of soda

Strauss (1927) suggested that the relief of pain was due to relief of pylorospasm Wilson (1928) found that filling the duodenal cap with barium by manual pressure was followed almost immediately by relief of pain Hurst (1929a) drew attention to the fact that when the stomach has partly but not completely evacuated its contents the pain differs from simple hunger in ceasing when the stomach is empty Horwitz Alvarez and Ascanio (1929) believed that the relief of pain after gastro enterostomy was due at least in part to the immediate removal of strain and overwork from the muscle in the

Wolf and Wolff (1943) found that substances like alcohol, hydrochloric acid, sodium hydroxide which have no effect on the normal mucosa, evoke pain of considerable intensity when the mucosa is inflamed, congested and oedematous They found that a contraction force of 35 mm Hg produces pain in the normal and only 20 mm Hg in the inflamed stomach Kinsella (1953) suggests that inflammation is the primary, motor function the secondary and acid the tertiary cause of ulcer pain

Hydrochloric acid

The observation that the removal of the acid factor abolishes ulcer pain has been brought forward in support of the view that hydrochloric acid is the primary cause of the ulcer pain, but closer investigation has thrown doubts on the validity of this argument

It has been observed that the mucous membrane of the stomach, whether intact or ulcerated, is insensitive to stimulation by dilute hydrochloric acid (Schmidt, 1909, Hurst, 1911, Baird, Campbell and Hearn, 1924, Wilson, 1928, Hardy, 1929, Christensen, 1931, Vanzant and Snell, 1932, Meyer, Fetter and Strauss, 1932, Kellogg, 1933, Alvarez, 1940, Bockus, 1943, Portis, 1944, Ruffin, Grimson and Smith, 1946, Smith, Ruffin and Baylin, 1947, and Doret, 1951) There appears no relation between symptomatic relief and effectiveness of neutralization (Wosika and Emery, 1936) and no correlation between healing and acidity (Bloomfield and French, 1938) The intra gastric acidity is not greatly different during periods of relapse and remission (Brown and Dolkart, 1937)

Palmer and Heinz (1934) on the other hand, believed that the presence or absence of the acid was the operative factor in ulcer pain Moore, Moore and Singleton (1934) believed that the pain was induced by direct irritation of the nerve endings by acid Bonney and Pickering (1946) advanced a similar view It will, however, be recalled that the floor of the ulcer is composed of two non nervous avascular strata, slough and granulation tissue (Askanazy, 1921), and the edges of the crater are covered by thickened mucosa and submucosa which are impermeable to the gastric acid (Kinsella, 1953) Bonney and Pickering s (1946) suggestion that the removal of a mucous scab from the ulcer by the solvent action of acid cannot be sustained because the mucus becomes more viscous by the action of acid and is soluble in an alkaline medium (Fontaine 1932, Bucher 1932, Webster and Komarov, 1932, Miller and Dunbar, 1933 and Mahlo, 1938) Furthermore, Wolf and Wolff (1948) observed the most copious secretion of mucus in response to hydrochloric acid (confirming Ochsner Gage and Hosoi, 1934) which they applied to the gastric mucous membrane of their fistulous subject

This reaction must be interpreted as a protective *réflèxe de défense*

Local tension

Local tension as a cause of ulcer pain has been suggested by Hurst (1911), Westphal and Katsch (1913) Ginsburg, Tumpowsky and Hamburger (1916), Carlson (1917), Hardt (1918), Miller and Waud (1925) Miller and Simpson

which overcome the stretch Variations of tonus change in smooth muscle take place without increased oxygen consumption and are usually pain less Furthermore, the peristaltic contractions of the stomach are intermittent but the ulcer pain is continuous although it may fluctuate in intensity The variations of the intragastric pressure are also intermittent the normal pressure being regulated by the intra abdominal pressure and the capacity of the stomach by the mechanism of "receptive relaxation

Ruffin, Baylin, Legerton and Texter (1953) who attempted the separation of the acidity and motility factors by maintaining the acidity at a high level by the administration of N/10 hydrochloric acid, observed that pain appeared with the onset of abdominal motility and ceased when motor function returned to normal The abnormality consisted of incoordinated activity of the antral evacuation mechanism with or without localised spasm Smith (1955), however could not correlate the production of pain by hydrochloric acid and its relief by sodium bicarbonate with changes of motility

The actual site of the ulcer pain appears difficult to establish That the ulcer itself is not the inherent cause of the pain is shown by the fact that the pain may be absent for prolonged periods although the ulcer itself is still present, and that ' ulcer pain may be present without a demonstrable lesion

The beneficial effects obtained by various types of treatment give some indication of the mechanism which may be involved in the production of peptic ulcer pain The relief obtained by the Sippy method cannot be ascribed entirely to the neutralization of the acid because this can never be completely achieved and sufficient account must be taken of the additional factor which is introduced by the frequent administration of both food and alkali

The relief obtained from the administration of food does not involve a specific element because all foods (even water) have the same beneficial effect, nor can it be claimed that a meal provides physiological rest for the stomach since the peristaltic waves are stronger at the beginning than at the end of a meal and hunger contractions although painful in nature are not qualitatively different from the digestive contractions The beneficial effect of the continuous drip methods can be ascribed to their action on the motor rather than the secretory functions of the stomach since the choice of the substance appears to be immaterial milk gives results essentially similar to alkalis The chewing of gum the swallowing of a stomach tube the mere act of deglutition and the passing of intestinal flatus all produce a transitory relief of pain

It may therefore be concluded that there exists one common feature which forms a link between all the above mentioned observations namely, that the pain disappears when the gastro-duodenal movement resumes its normal progression with the simultaneous return of the pyloric sphincter to its state of relaxation i e with the re establishment of isoperistalsis Since it is only the chronic ulcer which is associated with pain it may be argued that the factor which is involved in the causation of the chronic lesion may also be responsible for the pain which is associated with its activity

pyloric region Dragstedt and Palmer, (1932), by rubbing the serosa over the scar of a duodenal ulcer, produced deep circular contraction rings just distal to the ulcer which passed down the gut They also observed several peristaltic waves passing over the pyloric antrum at a time when no distress was experienced The arrest of the peristaltic wave coincided with the period when pain was recorded Kuntz (1946) believed that the pains are commonly alleviated when the pylorus is sufficiently relaxed to allow the gastric content to pass into the duodenum Bonney and Pickering (1946) concede that in duodenal ulcer pain the activity of the pylorus introduces an additional unknown factor Doret (1951) suggested a motor link—the gastro duodenal reflex—as intervening in the mechanism of pain production A cutaneous gastric reflex relaxes the pyloro duodenal spasm and re establishes the contraction of the stomach, the almost instantaneous effect being unaccompanied by a modification of gastric acidity

SUMMARY AND CONCLUSIONS

The theories which have been advanced to explain the mechanism of pain production in peptic ulcer will now be briefly examined before arriving at some conclusions

In respect of the chemical theory which indicts the acid factor as the main cause of the pain, it may be stated that while there is no ulcer pain in the absence of hydrochloric acid, as proved by the observation that the withdrawal of the gastric contents or its neutralization abolishes pain, it does not, however, explain why there are no significant differences in the gastric acidity during the periods of pain as compared with the painless intervals Gastric ulcer with hypersecretion may be present without pain The suggestion that excessive night secretion is responsible for nocturnal pain has been contradicted by many authorities While it is undoubtedly true that vomiting relieves pain because *it removes the acid, it must* also be admitted that motor activities are considerably reduced in the empty stomach—this may explain the relief following upon gastric haemorrhage A strong objection to the acid theory is provided by the difficulty of explaining the long latent period of pain after the reintroduction of acid into the stomach There appears to be a marked lack of correlation between the acid factor and the appearance of pain

Carlson (1917–18a) made the significant observation on a 25 year old medical student that although the volume of gastric juice and the free and total acidities were lower at the end than at the beginning of the experiment nevertheless *there was more bile in the stomach when the subject complained of pain*

In respect of the physical theory which inculpates a disordered gastric motility, there is no evidence that it is produced by the imbalance of the autonomic nervous system The muscular contractions of the empty stomach do not appear to be different in character from the contractions of the digesting stomach, nor is the tension of the muscle wall during a period of activity different from the tension during a period of quiescence Pain produced by stretching of the muscular wall is relieved by peristaltic contractions

Production of emboli

The production of emboli by injecting drugs into the gastric vessels includes the experiments with emulsion of wax (Panum 1862) lead chromate (Cohnheim 1890) and bismuth subgallate (Payr 1907 Chessine and Feldman, 1913, Grossi 1921) Bolton (1913) and Greggio (1916) refer to many other methods Ivy (1919b) had positive results with lead chromate but inert powdered charcoal gave negative results Positive results were obtained with injections of sterile oil into the omental vein (Wilkie 1911b) and by intravenous injection of small amounts of fat (Baronofsky Merendino, Bratrud and Wangensteen 1945 Friesen, Merendino Baronofsky, Mears and Wangensteen, 1948)

Ligation of vessels

Ligation of vessels failed to produce ulcers in rabbits (Muller 1860, Pavy 1863 Roth, 1869 Litten, 1875 Muller 1893 Fenwick, 1900, Turck, 1906, Clairmont 1908 Litthauer, 1909 Yano 1925, Bernheim 1932, Brenckmann 1932, Layne and Bergh 1943, Babkin Armour and Webster 1943) Berg (1947) produced ulcers in the antrum and in the fundus of the rat s stomach by ligating separately the vessels supplying these areas which have little or no collateral circulation

Occlusion of vessels

Occlusion of vessels—to prove Bergman s (1913) psychosomatic theory of the pathogenesis was carried out by the subcutaneous injection of drugs Among those used were pilocarpine with or without physostigmine (Westphal 1914), nicotine (Hayashi 1923), pilocarpine adrenaline and morphine (Nakashima, 1925) Localised pressure on the duodenal mucosa produced gastric lesions (Gallagher 1927 Underhill and Freiheit 1928) Haller (1920) declared that these results were not due to gastric spasm but to disturbances of the circulation and metabolism which resulted from the severe intoxication since he was able to produce similar lesions with morphine physostigmine and atropine which have an opposite physiological action

Portal insufficiency

Ulceration was produced by compression (Muller 1860 Fenwick 1900 Payr 1907), by ligation of the portal vein (Gunderman 1914) by Eck s fistula (Bollman and Mann 1927 Baronofsky and Wangensteen 1945)

General anaemia and local vascular insufficiency

Quincke (1882) and Ziromi (1910) suggested general anaemia and local vascular insufficiency as factors in the production of ulcer but the experiments of Silbermann (1886) Matthes (1893) and Litthauer (1909) contradict these results since they could prolong the acute ulcers only to a negligible degree with anaemia Brooks and Blalock (1934) found haemorrhage and

CHAPTER 8

THE EXPERIMENTAL ULCER AND ITS SIGNIFICANCE IN RELATION TO THE AETIOLOGY

A brief summary will be given of the methods which have been used in the production of artificial ulcer in order to assess their relevance to the aetiology of peptic ulcer Most of these experiments have generally been performed on dogs and the results obtained are not necessarily applicable to man because the nutritional factors, which are of primary importance in the diseases relating to the alimentary tract, are not the same It should be emphasized that peptic ulcers which are peculiar to man are not seen as a spontaneous manifestation in the dog As the number of experiments is considerable and the results often confusing and contradictory, even though the same experiment is performed on the same animal (Greggio, 1916), it is essential to adopt some basis for the classification of the lesions in order to provide a standard for comparison It is proposed, therefore, that the distinctive pathological features which have previously been described be adopted as a criterion for this classification and the terms of "acute", "chronic and 'anastomotic ulcer accepted in the restricted meaning as described in the chapter which deals with the Pathological Considerations Ulcers produced directly by trauma or indirectly by toxic agents will, therefore, be classified as "acute , whether they heal or whether they haemorrhage or perforate in the early stages of the experiment and in whatever situation they may occur, while ulcers produced by the juxtaposition of stomach and intestine will be classified as "anastomotic' and their chronicity as being due to the persistence of the initial trauma produced by the gastric juices on the intestinal mucous membrane Chronic ulcer will be restricted to ulcers which are situated in the "ulcer bearing ' area and which persist beyond the time limit usually allocated for the healing of acute ulcers these are accompanied by a diffuse inflammatory reaction and associated with hyperchlorhydria, the recognized manifestation of chronic ulcer

The subject of experimental ulcer has been reviewed by Bolton (1913), Langenskiold (1914) Greggio (1916), McCann (1929c), Lannin (1945), Berg (1949) and Ivy Grossman and Bachrach (1950)

INTERFERENCE WITH THE BLOOD SUPPLY

Applying Virchow s (1853) concept of vascular insufficiency as the cause of peptic ulcer several methods were used with the object of interfering with the normal blood supply to the stomach

streptococci obtained from chronic dental foci of infection which were similar to those of the patient from whom the cultures were obtained The results of experiments by Nickel and Hufford (1928) agree with those of Rosenow and confirm those of Haden (1925) and Haden and Bohan (1925) It should how ever, be noted that all these lesions were acute ulcers which did not develop into chronic ulcers

TOXIC AGENTS

Drugs and physical agents have been used systemically and locally in an attempt to cause ulceration Bolton (1913) referred to the use of various salts of mercury (Overbach, 1861, Bohm and Unterberger, 1874), cantharidine (Aufrecht, 1882), vegetable alkaloids (Pouchet 1899), phosphorus ergot, digitalis pilocarpine (Rehfuss 1909 Underhill and Freiheit, 1928, Light, Bishop and Kendall, 1932) nicotine (Hayashi 1917) and muscarine (Hay ashi, 1923) Elliott (1914) injected tetra hydro β naphthylamine subcuta neously into guinea pigs and acute ulcers formed within one or two hours if the stomach was kept filled with food, they healed within three days

Biological toxins

Anaphylaxis as a cause of ulceration was produced by Bolton (1910a) with gastrotoxin by Latzel (1913) with gastric juice, by Miyagawa Murai and Terada (1923) with immunized serum and by Shapiro and Ivy (1926) with non specific proteins

Anaphylactic ulcers have been produced by many Italian workers (Alessio, 1928 Coniglio 1930, Vallone 1930, Paolucci, 1931 Bernardini 1932 Culmone 1933 Guerrisi 1934) but Vallone (1930) has underlined that the anaphylactic ulcer does not resemble the human lesion in its histological characteristics Walzer, Gray Straus and Livingstone (1938) by the intra venous injection of the antigen could only obtain a transient oedema and hyperaemia of the gastric mucous membrane in monkeys previously sensi tized Friesen State Jasper Finn and Wangensteen (1948) produced oedema and haemorrhage with sensitized horse serum which in a few instances progressed to ulceration When histamine in beeswax was also given ulcera tion occurred regularly Wener Hoff and Simon (1948) who produced erosions with metacholin in beeswax over long periods suggested that the sequence of events was vascular stasis altered capillary permeability haemor rhage tissue anoxia and necrosis of the mucosa

TRAUMA

Lesions were produced by trauma to the abdominal wall by Wittneben (1886) Ritter (1887) Vanni (1889) Gross (1902) and Gibelli (1908–10) It is significant that all these authors reported that the lesion starts as a sub-mucosal haemorrhage Ivy Grossman and Bachrach (1950) relate these experiments to the acute gastric ulcers formerly common in young women and which might have been due to tight lacing Necheles and Olson (1942b)

necrosis of the duodenal mucous membrane following shock produced by bleeding the experimental animal Selye (1937) observed acute gastro-intestinal lesions in response to the alarm reaction (This subject is considered in greater detail in the section on Pathology) Penner and Bernheim (1939) gave large doses of adrenaline intraperitoneally in order to reproduce the vasomotor changes which occur in shock Lesions occurred in all parts of the digestive tract, varying from petechiae to large ulcerations (It is interesting to note that gastric devascularization has been advocated as the treatment for peptic ulcer Hey, 1937, Somervell 1945, and Visick, 1948)

BACTERIAL AGENTS

Bolton (1913) has reviewed the many methods which have been used in the production of ulcer by means of various bacteria they include the arterial injection of pus (Lebart, 1857, Cohn, 1860), the intravenous injection of *Bacillus pyocyaneus* (Charrin and Luffer, 1889), *B lacticus* (Wurtz and Sendet, 1887), *Staphylococcus aureus* (Letulle, 1888), bacillus of dysentery (Chantemesse and Widal, 1888), pneumococcus (Bezançon and Griffon, 1889), Pfeiffer s bacillus (Slatineano, 1890), diphtheria toxin (Enriquez and Hallion, 1893, Rosenau and Anderson 1907), feeding with *B coli* (Turck, 1907) Singer (1913), feeding rats on wet bread contaminated by faecal matter, produced acute ulcerative changes of the stomach after a fortnight Bolton (1913) pointed out that most of the authors stressed the fact that in the lesions produced there was very little or no inflammatory reaction

Particular attention has been focused on experiments on animals by Rosenow (1913), in which he produced acute ulcers by injecting streptococci intravenously and claimed some selective affinity of his strains for the gastric mucosa (elective localization), but Celler and Thalhimer (1916), who repeated these experiments, came to the conclusion that even though anhaemolytic streptococci are present in practically all gastric ulcers, this is not the factor which either initiates the ulceration or prevents it healing Hardt (1916) confirmed Rosenow s work Wilensky and Geist (1916) isolated streptococci according to Rosenow s technique, excised a piece of gastric mucosa and injected the organism into the defect at the time of operation The injection was repeated subsequently when it tended to heal The characteristics of chronic induration failed to develop in any ulcer and healing was not retarded Ivy (1919b) produced injury of the pyloric and duodenal mucous membrane and then fed cultures of virulent streptococci, only cachectic dogs developed lesions Rosenow (1921) stated that the strains obtained from acute ulcer, cholecystitis and especially appendicitis produced lesions more marked than those from the chronic forms of these conditions He pointed out that experiments to produce gastric ulcer by including bacteria in the food have been unsuccessful except in starving animals

Askanazy (1920) thought that the lesion was produced by *Oidium albicans*, but was unable to confirm this experimentally Kotzareff and de Morsier (1925) produced acute gastritis by injecting *Oidium albicans* for 20 days Meisser (1925) and Haden (1925) produced lesions in animals with

42), Zucker and Berg (1943), Zucker, Berg and Zucker (1945a, b), Berg (1946), Carlson and Hoelzel (1946), Jensen (1946), Freeman and Li (1946), Harris Hove, Mellott and Hickman (1947), Berg Zucker and Zucker (1949) See also Subnutritional Ulcer, p 105

CENTRAL NERVOUS SYSTEM

Lesions of the brain

Ebstein (1874) produced haemorrhagic lesions of the stomach intestine and lungs in the course of a few days by injury to the anterior corpora quadrigemina to the grey matter of the cervical cord and to the inner ear Hemisection of the cord at the level of the fourth cervical vertebra produced a deep duodenal ulcer in addition to extensive extravasations in the stomach Experimental production of gastro-intestinal haemorrhages and erosions by lesions of almost any part of the brain were obtained by Albertoni (1878) Ivy (1919 1920) observed haemorrhages and erosions in dogs after removal of large portions of the cerebral hemispheres cerebral peduncles optic thalamus and Ammon s horns Burdenko and Mogilnitzki (1926) and Oberling and Kallo (1929) produced multiple haemorrhagic erosions and occasionally perforation by stimulating the base of the brain immediately behind the infundibular stalk Erosions may be produced by electrical stimulation of the region of the tuberal centres in the infundibulum (Beattie 1932) injection of pilocarpine into the ventricles of rabbits (Light Bishop and Kendall, 1932) but not in monkeys (Ferguson 1936) hypothalamic injury in monkeys (Watts and Fulton, 1935 Hoff and Sheehan, 1935 1940, Martin and Schnedorf 1938), localized ablation of the cerebral cortex (Mettler Spindler, Mettler and Coombs 1936) injury of the hypothalamus in various regions (Keller, 1936a), introduction of foreign bodies into the third ventricle, hypothalamus optic thalamus corpus striatum and cerebral cortex (Hirata 1939) cerebral trauma (Cushing 1932, Tedeschi 1944 Strassmann 1947 Schacter and Schacter 1949) It is generally agreed that the lesions produced by trauma to the central nervous system are invariably of the acute type as they rapidly heal if the animal survives the experimental procedure

Sympathetic nerves

Dalla Vedova (1902) and Durante (1916) produced gastric lesions after injury to the sympathetic nerves Dalla Vedova found haemorrhages or necrotic lesions after section of the median but not the major splanchnic nerves Koennecke (1922–23 1926) and Alvarez Hosoi Overgaard and Ascanio (1929) after Billroth s operation and section of the splanchnics observed deeply penetrating jejunal ulcers

The coeliac plexus

Extirpation of the coeliac plexus with the object of removing the sympathetic action from the stomach and duodenum was claimed by some investigators to produce ulcers (Pincus 1856 Popielski 1903, Gundelfinger 1918

found that trauma in anaesthetized dogs did not affect gastric secretion and that its effects on gastric motility were slight and variable

Gastric erosions and ulcerations were produced by direct trauma to the stomach wall by heat (Decker, 1887), by cold (Sternberg, 1907), by porcelain tubes and direct destruction of the tissues (Ribbert, 1915) Quincke and Dattwyler (1875) found that acute gastric lesions in dogs, whether produced by pinching the mucous membrane with pincers, by tying up a fold with string, by excision of a portion of mucous membrane, by touching it with a hot iron, with silver nitrate, fuming nitric acid, or alcohol, or by submucous injections of silver nitrate or iron perchloride healed completely in from 5 to 21 days, according to the means employed and the severity of the lesion According to Ivy (1920a), exposure of the mucous membrane of the pyloric antrum to the exterior for 10 months causes no anatomical or physiological change Trauma caused by rough food in the stomach produced an ulcer (Bollman and Mann, 1927) but was not confirmed by Fauley and Ivy (1930) Anastomosis of the oesophagus direct to the duodenum did not produce ulcers (Ivy, Morgan and Farrell, 1931, Graves, 1935), but a rough diet in vagotomized rabbits produced ulcers (Beazell and Ivy, 1936)

X-rays

Ulcers may be produced by the exposure to x rays (Ivy, Orndorff, Jacoby and Whitlow, 1923, Ivy, McCarthy and Orndorff, 1924, Wolfer, 1926 a, b Aue and Ceculin, 1930, Engelstad, 1936, Palmer and Templeton, 1939) Betz (1947a) stated that the ulcer produced by x rays was preceeded by haemorrhagic necrosis of the mucosa following on capillary damage of an undetermined nature Some are acute ulcers which may perforate although a chronic type has also been described There is, however, unanimity on the observations that the effect of the x rays markedly depressed the gastric secretions It should, however, be remembered that the inflammatory changes lead to atrophy of the mucosa (Ricketts Kirsner, Humphreys and Palmer, 1948a, b, Ricketts, Palmer, Kirsner and Hamann, 1948, Douglas Ghent and Rowlands, 1950), and that Warren and Whipple (1923) have shown that the late effects of x radiation are atrophy, proliferation, metaplasia and fibrosis of the gastric mucous membrane The use of beta rays (Douglas Ghent and Rowlands 1951) in the treatment of peptic ulcer must impose the exercise of the greatest caution

DEFICIENCY STATES

Experimental ulcers following various forms of deficiency diets and inanition have been reported by Turck (1906) McCarrison (1921), Pappenheimer and Larimore (1924), Sun (1926) Hoelzel and Kleitman (1927), McCarrison (1931b), Moore and Plymate (1932), Dalldorff and Kellogg (1932) Sure and Thatcher (1933) Manville (1933), Olcott (1933), Smith and McConkey (1933), Almquist and Stokstadt (1935), Howes and Vivier (1936) Hoelzel and Da Costa (1937) Weech and Paige (1937), Orr and Rao (1939) Dogra (1941), Dyer and Roe (1941) Chen (1941) Morris and Lippincott (1941–

their role In order to clarify this subject it is essential to differentiate their effect (a) on the stomach and first part of the duodenum (the 'ulcer bearing area), and (b) on the intestine below the entrance of the common bile duct into the duodenum

Effect of acid and acid pepsin on the gastric mucous membrane

Many investigators have in addition to other methods of interfering with normal function of the stomach administered different strengths of hydrochloric acid in an attempt to produce a lesion in the stomach Since it is generally admitted that hydrochloric acid plays an essential role in the causation of the chronic lesion, this subject is discussed in detail in the section which deals with the Pathogenesis, where reference is made to the experiments of Samelson (1879) Ewald (1879), Matthes (1893) Ruzicka (1897) Saitta (1900) Frouin (1908, 1910), Moutier (1910), Bolton (1910), Lichtenbelt (1912), Bolton (1913), Friedman and Hamburger (1914) Greggio (1916) Dragstedt (1917), Ivy and Oyama (1921) Silbermann (1927) Gallagher (1928b), Brenckmann and White (1929), McCann (1929a), Puhl and Brodersen (1931) Buchner and Schneider (1931), Puhl (1932) Matthews and Dragstedt (1932) Mann and Bollmann (1932) Overgaard (1931 1934) Ochsner, Gage and Hosoi (1934) Orndorff Bergh and Ivy (1935) Stevens (1935) Howes Flood and Mullins (1936), Schmidt and Fogelson (1937) Matzner and Windwer (1937) Wangensteen Vargo Hay Walpole and Trach (1940), Schiffrin and Warren (1942), Wolf and Wolff (1942b) Shay Komarov, Fels Meranze Gruenstein and Siplet (1945) Friesen Baronofsky and Wangensteen (1946), Cummins Grossman and Ivy (1946) Stein Grossman and Ivy (1947) Fogelman Grossman and Ivy (1949) and James and Pickering (1949)

It may be stated emphatically that there is no evidence whatsoever that a chronic lesion has been produced experimentally by hydrochloric acid or by the pepsin hydrochloric acid combination in the acid bearing area which in any way resembles the chronic ulcer in man

Pepsin as an element in the causation of peptic ulcer was suggested by Soupault (1906), Mathieu (1913) Hayem and Lyons (1913), Schiffrin (1940), Schiffrin and Warren (1941 1942) Shay Komarov Siplet and Gruenstein (1947) and Le Veen (1947) These views were contradicted by the results of experiments (Driver Dozier and Denham 1943 Driver Chapell and Carmichael 1945 and Driver 1945a)

Effect of gastric juice on the intestinal mucous membrane

The susceptibility of the gastro-intestinal tract to hydrochloric acid has been shown in many ways Matthes (1893) observed that the upper part of the intestine was less sensitive to the action of hydrochloric acid than the lower part Ivy and Oyama (1921) observed that perfusion of a pouch of the pyloric antrum with 0 1 N HCl had no effect but significantly it caused bleeding of the jejunal mucous membrane Ivy and McIlvain (1923) observed

Lium, 1941) Lillehei and Wangensteen (1948) observed that post ganglionic sympathetic denervation appears to have much more severe effects than pre ganglionic denervation Alvarez (1948) stated that the operation is difficult, injury to other structures cannot be avoided, and considerable shock is responsible for the high mortality of animals He thinks that there appears to be no clinical evidence that splanchnicectomy, which has been in vogue for the treatment of hypertension and other conditions, has caused the appearance of a peptic ulcer

The Vagi

There are many contradictory reports dealing with the production of gastric lesions from interference with the vagus nerves Positive results were produced by faradic stimulation of the left peripheral end (Talma, 1890), sub diaphragmatic vagal section (Van Yzeren, 1901, Ophuls, 1906, Ziron, 1910, Lichtenbelt, 1912, Finzi, 1913, Latzel, 1913, Antonini, 1914, Greggio, 1916, Gundelfinger, 1918, Keppich, 1921, Beaver and Mann 1931, *Stahnke, 1924, Alvarez, Hosoi, Overgaard and Ascanio, 1929*, Beazell and Ivy, 1936, Ferguson, 1936, Manning, Hall and Banting, 1937) Donati (1904) and Kobayashi (1909) had negative results

Ivy, Grossman and Bachrach (1950) concluded, from a summary of the more reliable data on vagotomy in rabbits, that the incidence of true ulcer is considerable, but the literature concerning the development of ulcer in dogs, is less contradictory, the results having usually been reported as negative, occasionally as doubtfully or convincingly positive

GLANDULAR INFLUENCES

The effect of glandular activity on the formation of ulcer may be viewed as being associated with some type of nervous mechanism

Lesions following insufficiency of hepatic function induced by partial hepatectomy were observed by Bollmann and Mann (1927) Acute lesions in the stomach and duodenum following bilateral adrenalectomy were reported by Gibelli (1908), Finzi (1913) Elliott (1914), Friedman (1915) Mann (1916), Ivy (1920a), Katayama (1920), Banting and Gairns (1926), Levy and Armingeat (1930), Freud Luwisch and Oestreicher (1935), and Imperati (1936)

Removal of the thyroid and parathyroid proved, on the whole, to give negative results (Carlson and Jacobson, *1911*, Silvestri *1920* Keropian, *1925*, *Winkelstein and Ziegler 1930*, *Wu, 1945*)

Injection of pituitrin produced erosions (Dodds Noble and Smith, 1934, Dodds Hills, Noble and Williams, 1935, Berg 1942 Baronofsky and Wangensteen 1945 b) but little effect was observed by Atkinson and Ivy (1937), Gross, Ingram and Fugo (1941) and Nedzel (1943)

DIGESTIVE JUICES

The importance of the digestive juices in relation to ulcer has long been suspected and many investigations have been made in an attempt to define

a chronic peptic ulcer by this method Schur and Plaschkes (1914–15) did not support Stuber's view they believed that pepsin in the presence of hydrochloric acid produced a peptic ulcer Greggio (1916) who repeated Stuber's experiments was unable to confirm his results However it is significant that by enlarging the pylorus and allowing pancreatic juice to enter the stomach by the method of Stuber, which at the same time allowed the regurgitation of bile Greggio produced inflammatory reactions both in the duodenum and the stomach and considered that, although this method did not produce peptic ulcer, the time factor (90 days) may not have been sufficiently long to achieve these results Elman (1928) pointed out that the pancreatic juice played an important role in the neutralization of gastric acidity and therefore, in the prevention of chronic ulcer

Suppression of the pancreatic secretions — Ligature of the pancreatic duct or pancreatectomy by suppressing the pancreatic secretions produced gastric, duodenal or jejunal ulcers according to Jona (1918) Ivy and Fauley (1931), Bauer and Aron (1933) and Bachrach, Schmidt and Beazell (1939), but no lesions were observed by Berg and Zucker (1932) Berg (1934), Loewy (1935) and Boyce and McFetridge (1938)

External pancreatic fistula — The total loss of secretions gave positive results according to Elman (1931), Elman and Hartman (1931) and Matthews and Dragstedt (1932) but only occasionally according to Berg and Zucker (1932) Loewy (1932) and Berg (1934)

Internal pancreatic fistula — After transplantation of the pancreatic duct into the terminal ileum in dogs, no ulcers were observed by Owings and Smith (1931–32) Graves (1935), Deloyers (1936), and Craft (1938) Drainage into the ureter gave no ulcer (Loewy 1932) Drainage to the anastomosed jejunum produced ulcers (Leriche, Fontaine and Hermann 1931) Ivy, Grossman and Bachrach (1950) suggest that the discrepancies in the literature regarding the incidence of duodenal ulcer in dogs having a pancreatic fistula or exclusion of pancreatic juice are undoubtedly due to differences in the state of nutrition and acid base balance of the animals

Bile

Three types of experiments may be distinguished in respect of the lesions produced by methods in which the bile factor is concerned (1) methods producing biliary obstruction (2) biliary elimination and (3) the direct effect of bile on the gastric mucous membrane

Obstruction of the bile flow

Ligation of the common bile duct and the portal vein produced haemorrhages and erosions of the stomach and duodenum, with renal gastrointestinal and cerebral manifestations (Gundermann 1914 Kleeblatt, 1914, Hosomi 1928 Berg, 1930 Bollmann and Mann 1932 Dostal and Andrews 1932 Ivy, Schrager and Morgan 1933 Halpern, 1933 Nakashima 1934, Iesu, 1937 Horrall 1938)

that in a Thiry fistula of the upper jejunum bleeding occurs after 15–30 minutes perfusion with 0 1 N HCl

McMaster (1934) made end to end anastomosis between the pyloric end of the stomach and progressively lower levels of the intestine from the duodenum to the colon The intestinal mucosa was observed to be increasingly sensitive to gastric contents from the duodenum to the colon Florey and Harding (1934) found that the gastric mucosa was undamaged by 0 1 N HCl, the first part of the duodenum was damaged by 0 1 N HCl but withstood 0 05 N HCl The jejunum was severly damaged by 0 05 N HCl

That the upper intestine is more resistant to the corrosive action of gastric juice than the lower segments was observed by Harper (1932, 1935), Matthews and Dragstedt (1932), Ochsner, Gage and Hosoi (1934), Graves (1935), Florey, Jennings, Jennings and O'Connor (1939), Kolouch (1945), and Lannin (1945)

Grossman and Fogelman (1948) observed that 0 10 N HCl with 2 per cent pepsin produced severe acidosis (blood pH 6 9–7 2) and gastro-duodenal ulceration within 3 days When sufficient $NaHCO_3$ was added to maintain normal blood pH no ulceration developed, but when the acid mixture was raised to 0 15 N HCl ulcers developed The threshold of acid concentration for ulcer production was, therefore between 0 10 and 0 15 N

Dragstedt, Oberhelman and Smith (1951) produced typical gastro jejunal ulcers in animals in which the antrum was transplanted into the colon as a diverticulum, and intestinal continuity re established by gastro jejunostomy

The action of the pepsin hydrochloric acid combination on the gastric mucous membrane raises the question of autodigestion as a factor in the causation of ulcer and is discussed in the relevant chapter under Pathogenesis (p 241)

Proteolytic enzymes

Driver (1945a, b) observed that the proteolytic enzymes, rennin, trypsin and erepsin, under hydrostatic pressure of 90 cm H_2O produced necrosis of the intestine in dogs rennin being the most active of the three—neither steapsin, nor amylopsin caused necrosis

Pancreatic juice

Action of pancreatic juice on the gastric mucous membrane — Stuber (1914) attempted to produce ulceration by enlarging the pylorus and producing a pyloric insufficiency in order to facilitate the reflux of pancreatic juice into the stomach To prevent interference with the action of the pancreatic enzymes by the hydrochloric acid he added alkalis to the diet which consisted of milk, water bread and potatoes and he claimed that in this way he produced small ulcers in dogs The lesions were generally haemorrhagic erosions, where they were penetrating ulcers the edges were flat and there was no generalized inflammatory reaction As a control for his experimental procedures (12 dogs in all) one dog was fed on a meat free alkaline diet and *half a teaspoonful of pancreatic juice* each day, he claimed to have produced

former It was found early in the series of experiments that the gastric mucous membrane of the dog showed a greater resistance to injury produced by bile and hydrochloric acid than did the stomach of the cat. This was due in part to the presence of abundant mucus frequently found in the dog s stomach and to active secretion of mucus which often quickly followed the introduction of bile and acid into the dog's stomach'

The application of bile and hydrochloric acid to the stomach was performed in several ways

(*a*) By direct application to the gastric mucous membrane after the anterior wall of the stomach had been incised during an operation (*b*) by stomach tube (*c*) after opening the abdomen by *injecting into the stomach* bile and acid through an aspirating needle passed through the wall of the stomach (*d*) by injecting bile and acid backward into the stomach through the pylorus by means of an aspirating needle, passed through the wall of the duodenum, (*e*) by anastomosing the gall bladder with the stomach after ligating the common bile duct and subsequently introducing acid into the stomach of the animal by means of a stomach tube

Bile was injected through the wall of the duodenum at the level of the entrance of the common bile duct and in the direction of the pylorus It was allowed to flow back slowly through the pylorus into the cavity of the stomach traversing in this way the region of the gastro-intestinal tract which it would naturally take in the case of ordinary regurgitation into the stomach The method allowed the use of the animal s own bile which could be obtained by aspiration from the gallbladder no handling of the stomach being necessary in this experiment Numerous control experiments were made under conditions identical with those of the best experiment

The experimental observations were as follows If the mucous membrane of the stomach of the cat or dog be exposed by operation and a drop of bile previously removed by aspiration from the gall bladder, be placed upon its surface the bile causes no marked change in the appearance of the mucosa If a drop of 0 5 per cent of hydrochloric acid be placed by means of a pipette upon the mucous surface of the living stomach no striking changes in the appearance of the epithelial surface occur No gross or histological injury of the tissue is produced under these circumstances by either bile or hydrochloric acid providing the tissues are handled with care and receive no trauma When however a drop of bile is placed on the mucous surface of the stomach and immediately afterwards a drop of 0 5 per cent hydrochloric acid is added to it there soon appears at the surface of the epithelium evidence of well-defined reaction consisting in the formation of a yellowish or greenish-yellow precipitate which corresponds in outline to the area occupied by the combined drops of bile and acid The relative quantity of mucus appears to be an important factor in determining how closely in contact with the epithelium the interaction of bile and acid is to occur

As early as three hours after the injecting of bile and hydrochloric acid into the stomach of the cat during a late period of digestion injury to the mucous membrane may be observed

Elimination of bile

Elimination of bile by external biliary drainage produces gastric and duodenal ulcer (Koelliker and Müller, 1856, Kehrer, 1914, Grey, 1919, Mann and Williamson, 1923, Hoffman, 1927, Pecco, 1931, Kim and Ivy, 1931, Berg and Zucker, 1932, Amorosi, 1933, Donati and Cavazza, 1934, Fiessinger and Palmer, 1935, Hawkins and Whipple, 1935, Hawkins and Brinkhous, 1936, Hanke, 1937)

Hooper and Whipple (1916) pointed out that bile fistula dogs died from symptoms of intoxication, and Whipple (1932) that bile is essential to life Anastomosis of the gallbladder to the right renal pelvis and ligation of the common bile duct produces ulcers (Kapsinow, Engle and Harvey, 1924, Kapsinow, 1926, Berg, Johnston and Jobling, 1927, Deloyers, 1936, Cornil, Imbert and Mosinger, 1936)

Feeding of bile to animals causes the ulcer to heal or may prevent its formation (*Blanck, 1935, Bachrach, Schmidt and Beazell, 1939*)

Action of bile on the gastric mucous membrane

The experiments which refer to this subject will be dealt with in some detail as they are of primary importance in the author s theory of the patho genesis of the chronic ulcer

Roehrig (1863) noted ecchymoses in the gastro intestinal tract following administration of bile salts Rywosch (1891) administered 25 mg of bile to chickens for 3 days which resulted in diarrhoea and death on the fourth day At autopsy the mucous membrane of the crops showed necrosis and death was attributed to the direct inflammatory action of the bile Fifty cc of a 10 per cent solution of ox bile administered to rabbits for 3 days caused marked inflammation of the stomach and death within 4 days

Sellards (1909) produced large haemorrhagic areas in the stomach and ulcerations of the mucosa by the intraperitoneal injection of sodium glyco-cholate Similar lesions were produced by the subcutaneous injection of bile or bile salts small repeated doses tending to localize the ulcers near the pylorus Since there were only minute lesions in the lungs and intestines, he claimed that bile salts had a specific action on the gastric mucosa Bolton (1913) stated that bile salts and formaldehyde in dilute solution produce a marked vascular reaction in the stomach, the mucous membrane is of deep red colour and there is a great increase in the secretion of mucus These effects are produced by a 3 per cent solution of sodium taurocholate and by an 0 3 per cent solution of formaldehyde, weaker solutions are inert

Smith (1914) produced lesions of the mucous membrane of the stomach which varied from simple hyperaemia and small haemorrhages to small ulcers, by injecting 5–10 cc of the animal s (dog and cat) own bile in conjunction with 0 5 per cent hydrochloric acid (the animal s normal gastric acidity) into the stomach via the duodenum

These experiments are sufficiently conclusive to warrant a more detailed quotation

'The animals used for experiments were the cat and the dog, chiefly the

constriction The duodenal mucous membrane showed ulcerations in front and behind the stenosis in the zone of stasis These lesions were different from those seen in the dog which are produced by ascaris worms The lesion was small and had the appearance of a fissure and could be identified by the presence of a small haemorrhagic focus All animals had subpyloric and perigastric ganglionic infarcts The authors could not explain the cause of the grave cachexia which was present

Tashiro (1931) confirmed these findings and reported that the action of bile acids is antagonized by phosphatides, cholesterol oleate and other lipids He believed that substances which produce ulceration of the gastric mucosa in guinea pigs reduce the phosphatide content of the blood and thus remove this protection from the bile salts Bert (1933) refers to the observation of de Beule who effected a cure of the ulcers associated with duodenal stasis by duodeno jejunostomy in cases which had resisted gastro-jejunostomy He could not reproduce the results obtained by Slocumb (1927) when he applied an incomplete ligature of the duodeno jejunal angle or by ascending or descending invagination of the bowel Figurelli (1933) found that artificial stenosis of the bowel was not efficient, for a long time the duodenum dilated above the stenosis and became recanalized after 2 or 3 months If the stenosis persisted, it produced inflammatory reactions Trincas (1933) observed that feeding with thyroid gland and bile salts induced ulceration and Schmidt (1933) found that the ulcerative effect of bile salts was increased by feeding with thyroxine and inhibited by lecithine Anderson and Farmer (1934) observed that injection of bile salts in guinea pigs (0 1 g) caused death and extensive ulceration of the gastric mucosa, 3 animals perforated In rats death occurred in 24 hours but no ulceration was seen similar to that in the guinea pig Oda (1936) who fed ox gall to rabbits with artifically produced gastric mucosal lesions found that healing was delayed, 10 g had a more marked effect than 5 g There was atrophy of the stomach wall and gastric mucosa Yoshitomi (1935) found that when the isolated stomach of the rabbit was perfused with a solution of sodium taurocholate, ulceration resulted which was intimately related to the acidity of the gastric content and that bile could not produce ulcers in the absence of free hydrochloric acid Fujioka (1937) confirmed these results but stated that bile salts could produce ulcers by direct contact with the gastric mucosa He stated that fresh human bile, which produced ulcers contains 100 times the minimal dose of sodium taurocholate and that mucin from the salivary glands has an inhibitory effect Lecithine mucin and serum albumin have properties of forming compounds which neutralize the action of bile He suggested that provided there is sufficient mucin in the stomach no ulcer forms

In view of the conflicting reports and the fact that the neutralizing effect of bile upon gastric acidity has been given by most investigators as the explanation of the appearance of ulcers after exclusion of bile, Driver and Carmichael (1945) exposed isolated loops of intestine in dogs to acid pepsin solutions with and without bile salts at zero and 90 cm H_2O pressure and at a *p*H of approximately 1 2 and 3 7 They found that bile salts markedly in-

'In experiments where the stomach was sutured to the anterior parietal peritoneum, to cause a retention of bile and hydrochloric acid in the stomach by impairing peristaltic movements of the stomach and delaying evacuation, unusually severe injuries to the gastric mucous membrane occurred

'In the course of experiments in which the stomach was opened and bile and acid applied to the mucous membrane, it became apparent that lesions were most apt to occur when digestion was in progress and gastric juice was present in the stomach With an empty stomach, and especially after a period of fasting, injury to the mucous surface did not occur It is noteworthy to emphasize that when these experiments were performed during digestion, lesions occurred chiefly between the third and the fifth hour after feeding, when mucus is probably less abundant in the stomach than in the earlier stages of digestion

"In experiments in which bile and hydrochloric acid were confined to the fasting stomach in the presence of moderate amounts of acid infusion of gastric mucous membrane, lesions were produced

'In experiments controlling the above, in which animals had been starved for 24 hours, and had received hydrochloric acid and the gastric juice but not bile, lesions did not result'

Sweet, Buckman, Thomas and Bell (1923) made several attempts to produce an artificial stasis either by a mild volvulus or by fascial bands and by the production of a blind loop, with drainage through the distal segment, from a point above the loop or from the stomach In the latter method the duodenum was sectioned at a level about 25 cm from the pylorus and the proximal end carried back to be introduced into the duodenum above the end to end anastomosis The distal end was then introduced into the duodenum, above the blind loop in some cases, in other cases into the stomach The purpose of the operation was not to produce an absolute obstruction but to establish a chronic functional obstruction, where stasis and a source of toxaemia might be set up No indication is given as to the time factor of the experiments In only a few isolated cases were suggestions of an ulceration present These were seen as localized haemorrhagic areas in the mucous membrane, and in one case, on the lesser curvature in the pyloric antrum of the stomach The authors, nevertheless, concluded that their results must be acknowledged to be negative

Slocumb (1927) produced ulceration of the stomach and duodenum in a large percentage of cases in dogs, by establishing partial obstruction of the duodenum for a considerable period of time The method used was as follows the duodenum was doubled upon itself and sutured in such a way as to present a flattened S-shaped curve the result of which was partial obstruction amounting to 75 per cent or more It is noteworthy that where the ulcers healed, this occurred as soon as the lumen of the duodenum became unobstructed Del Valle and Brian (1928) produced stenosis of the duodenum in 8 dogs by placing ligatures 15 cm below the pylorus 4 of the animals succumbed early, 2 died of cachexia after 3 or 4 months, and 2 survived 9½ months They observed dilatation and muscular hypertrophy above the

cosa Similar results were observed by Kehrer (1914), Langenskiold (1914), Grey (1919), Keppich (1921), Mann and Kawamura (1922) and Dott and Lim (1923)

Mann and Williamson (1923) who isolated the duodenum by closing its pyloric end and anastomosing its distal end to the distal part of the ileum and the free end of the jejunum to the pylorus (the so called M W operation of surgical duodenal drainage), found a high percentage of ulcers They were situated one or more millimeters from the gastro jejunal anastomosis on the intestinal side of the stoma, no ulcer arising in the stomach itself Similar results were obtained by Lameris (1924), Morton (1927), McCann (1929c), Neuman Demoor and Deloyers (1930a, b, c), Neuman, Deloyers and Demoor (1931), Pecco (1931), Jenkins and Palmer (1931), Owings and Smith (1932) Matthews and Dragstedt (1932), Fontaine and Kunlin (1932a), Goldberg (1932b), and Volini, Widenhorn and Finlayson (1937)

No ulcers were formed when the drainage was directed to the duodenum (Winkelbauer and Starlinger 1926, Gallagher and Palmer 1933 Palma, 1935, McMaster 1935 Harper, 1935, Kunlin and Cavalli, 1936, Slive, Bachrach and Fogelson, 1940)

Denutrition and cachexia as the cause of death were suggested by Deloyers (1936), Flood and Mullins (1936), Wilhelmj O Brien McCarthy and Hill (1936), Orndorff Fauley and Ivy (1936), Shoch and Fogelson (1941), Oliver (1947 1949), and Visscher and Lyster (1949)

Hands Fauley, Greengard Preston and Ivy (1941) at first reported that enterogastrone was an effective agent in the prevention of the development of gastro jejunal ulcers but subsequent experiments showed that enterogastrone did not prevent ulcer formation in Mann Williamson dogs

CINCHOPHEN ULCER

The cinchophen ulcer was first produced by Van Wagoner and Churchill (1932) Cinchophen was administered to 3 groups of dogs which received respectively 27 10 and 5 times the human dose, with ulcer formation in all cases in a fourth group which received the normal human dose only 4 out of 7 had ulcers Early symptoms were anorexia, nausea vomiting and tarry stools

That the toxic effect of cinchophen was the cause of the ulcer was shown by Churchill and Manshardt (1932), Barbour and Fisk (1933), Bloch and Rosenberg (1934) Schwartz and Simonds (1934), Bollman and Mann (1935), Stalker, Bollman and Mann (1937) Simonds (1938), and Reymont (1940)

The formation of ulcers was prevented by the administration of mucin (Deloyers 1936, Reid and Ivy 1936, Stalker Bollman and Mann 1936, Morrison, 1945 Winters Peters and Crook 1939) Chiray Justin Besançon Debray and Bourgeois (1942) produced healing and recurrence of cinchophen ulcers by the administration and withdrawal of pectin (which is physically and chemically similar to mucin)

That the ulcer was not due to acid was shown by Neuwelt and Necheles (1940) and Davis, Bradley Bachrach and Ivy (1940)

hibited the digestive action of pepsin on intestinal mucosa at a *p*H of 1 25 At a *p*H of 3 7 there was no damage to the mucosa regardless of hydrostatic pressure or the presence of bile salts

It should be noted that positive results were obtained when the *p*H was 1 25 but they did not occur when the *p*H was 3 7, since a *p*H of 1 2 corres ponds to 0 1 N HCl concentration while 3 7 corresponds to 0 0003 N HCl concentration, it will be realized that the latter solution is considerably weaker than the former and that much of the damage produced can be *ascribed to the concentration of the acid itself acting on the intestinal* mucosa which is adapted to the action of bile but not of acid pepsin solutions

(The role of bile as a factor in the causation of chronic ulcer in man is considered in detail in the Section of the Pathogenesis)

The anti gizzard erosion factor — Reference is made to the anti gizzard eros ion factor only to point out that there appears to be no evidence that it is in any way related to the problem of peptic ulcer in the human Bile or bile acids in the diet of chicks prevents the lesions (Almquist, 1938), and cholic acid or dehydrocholic acid appear equally effective (Almquist und Mecchi, 1938, Hegstedt, Hier, Elvehjem and Hart, 1941) Whole and skimmed milk, protein free milk and whey, reduce the incidence and severity (Almquist, Mecchi and Kratzner, 1941–1943) Hog's bile, which contains very little cho lic acid, is comparatively ineffective (Hanson and Grossman, 1950)

Cheney (1938) observed that chicks which developed gizzard erosions secreted, in response to histamine, gastric juice with an average acidity 16 8 *degrees higher than normals and 24 3 degrees higher than those on a deficient* diet which did not develop erosions, but Dam and Segal (1945) found the fasting secretion of normal chicks more acid than the secretion of chicks reared on various artificial, including the ulcerogenic, diets, and the fasting acidity on ulcer producing diets was no higher than on normal diets

According to Ivy, Grossman and Bachrach (1950), who believe that the lesion is the result of a dietary deficiency, there is evidence that gizzard lesions are a normal accompaniment of the development of chicks for haemorrhages appear in the gizzard of embryos by the twentieth day of incubation, and gizzard lesions are only exceptionally absent in day old chicks and usually do not progress in severity during the first week regardless of the diet

SURGICAL EXCLUSION OF THE DUODENAL SECRETIONS

Bickel (1909) excised the duodenum, transplanted the bile and pancreatic ducts into the abdominal wall and restored the continuity of the gut by joining the stomach to the jejunum The animal died 4½ weeks later from a perforated jejunal ulcer, there were 4 more anastomotic ulcers present Exalto (1911) who first performed a gastro enterostomy with exclusion according to the method of von Eiselsberg obtained no ulcers, but when he performed the exclusion operation with a Y anastomosis according to the method of Roux ulcers were produced With implantation of the duodenum into the colon, an ulcer was formed in every case He concluded that the ✓ ulcers were formed by the action of hydrochloric acid on the intestinal mu

(1940), Hay, Varco Code and Wangensteen (1942) and Shoch and Fogelson (1942) Surgical confirmation of the acid theory was attempted by Andrus Lord and Stefko (1943), who reported that the jejunal graft caused a reduction in gastric acidity Lannin Hay, Judd and Wangensteen (1944) have shown that an extensive (75 per cent) gastric resection protects histamine in beeswax ulcer Baronofsky, Lannin, Sanchez Palomera and Wangensteen (1945) found that small gastric resections (25 and 50 per cent) in dogs when accompanied by no afferent loop (Billroth I) give a high incidence of histamine ulcer, when 75 per cent of the stomach was removed no ulcer formed A short afferent loop (Billroth II) does not protect against histamine ulcer Kolouch Castellanos Moreno, Dubus Baronofsky and Wangensteen (1945) stated that a long afferent duodeno jejunal loop invites stomal ulcer in any gastric operation carried out on the Billroth II plan of procedure Baronofsky Friesen, Sanchez Palomera, Cole and Wangensteen (1946) found that bilateral vagotomy (infradiaphragmatic and supradiaphragmatic) failed to protect against ulcer and erosions (gastric or duodenal or both) produced by chronic histamine action in the dog cat and rabbit Schilling and Pearse (1948) produced acute and chronic ulcers after subtotal gastrectomy Fast Friesen and Wangensteen (1947) found that the Sippy regimen of frequent feeds of milk and alkaline powders succeeded in suppressing the deep ulcer but that gastro-enterostomy the small gastric resection and the Schmilinsky operation offer no protection

LeVeen (1948) noted that the typical ulcers in the first portion of the duodenum ordinarily induced by the histamine in beeswax method did not occur in animals who had undergone a devascularization operation However, with extensive ligation ulcers occurred in the mid portion of the greater curvature of the stomach Baronofsky (1948) found that the ligation of the large arteries of the stomach and additional small arteries from the gastro-epiploic vessels failed to prevent histamine provoked ulcer

Eppinger and Leuchtenberger (1932) have shown that the histamine lesions start with oedema and according to Heinlein and Kastrup (1938) the initiating factor in histamine gastritis is not the acid but the direct toxic action Merkel (1942) described oedema of the mucosa which also involved the deeper tissues The mechanism of histamine ulcer has been ascribed by Code (1952) to the corrosive action of the continuously secreted gastric juice However Ivy Grossman and Bachrach (1950) concluded from a review of the subject that it cannot be unequivocally assumed that the histamine ulcer is due to the corrosive action of the gastric juice alone

Cox and Barnes (1945) observed that an increase in the number of parietal cells occurs in the mucosa of the guinea pig stomach after protracted stimulation with histamine over a period of 2–4 weeks They considered that this is presumably a hyperplasia and may indicate a mechanism to explain differences in the number of secreting cells in different human stomachs

None of the anti histamine drugs have shown a significant inhibitory effect on the gastric stimulating action of histamine (McElin and Horton, 1945

Antituitrin S and posterior pituitary extract had little effect in preventing occurrence of the ulcer (Farbman, Sandweiss and Saltzstein, 1939, Slutzky, Wilhelmj and Stoner, 1941)

Hyperchlorhydria is not an associated phenomenon of the cinchophen ulcer and, therefore, cannot be considered as being related to the chronic form of ulcer as seen in man

HISTIDINE

Weiss and Aron (1933c) argued that the ulcer produced by the Mann Williamson operation was due to the insufficiency of certain amino-acids and the consequent reduction in the resistance of the tissues to the corrosive action of the gastric juices, and they claimed that the injection of histidine prevented ulcer formation Barry and Florey (1936) showed, however, that histidine was incapable of preventing ulcer formation, and similar conclusions were arrived at by Flood and Mullins (1936), Sandweiss, Saltzstein and Glazer (1937), and Wu (1937)

HISTAMINE ULCER

Buchner and Molloy (1927) produced ulcer in the fore stomach in about 33 per cent of rats with doses of 6–12 mg of histamine per 100 gm of body weight Atropine in 0 5 mg doses did not inhibit ulcer formation Buchner, Siebert and Molloy (1928) noted an increased incidence of ulcer by starving the animals on alternate days The results were not altered by dividing the vagi (Burkle de la Camp, 1929) Positive results were obtained with histamine by McIlroy (1928), Matsueda (1931), O Shaughnessy (1931) Overgaard (1931), Harde (1932), Eppinger and Leuchtenberger (1932), Friedenwald, Feldman and Morrison (1933), Carnot, Simonnet, Tissier and Cachera (1933a, b), Flood and Howes (1934) Ochsner, Gage and Hosoi (1936), Heinlein and Kastrup (1938), Merkel (1942), and Marconi and Costa (1951)

Orndorff, Bergh and Ivy (1935) injected one group of dogs every two hours with pilocarpine, a second group with histamine, and a third group with both pilocarpine and histamine Acute lesions of the stomach and duodenum were observed in the 3 types of experiments but no chronic or perforating ulcers were produced

The toxic element in the production of the lesion was shown by Lannin (1945) and Baronofsky and Wangensteen (1946)

Grossman, Dutton and Ivy (1946) observed that 100 mg of enterogastrone concentrate fails to protect dogs with histamine induced ulcers Lillehei and Wangensteen (1948) found that post ganglionic sympathectomy of the gastro-intestinal tract potentiates the susceptibility of the histamine induced ulcer in dogs

Histamine-beeswax ulcer

Code and Varco (1940) introduced the histamine and beeswax technique to study the effect of the prolonged action of histamine in order to produce chronic effects and observe the features of chronic histamine poisoning These experiments were enlarged by Walpole Varco, Code and Wangensteen

stomach to the jejunum It is usually single, the site of the lesion is in the path way of the outflow of the gastric content never in the fundus It starts on the surface of the mucosa as a greyish circumscribed membrane Grossly and microscopically this type of lesion resembles the chronic peptic ulcer as found in man The cinchophen ulcer is considered by Mann to correspond to the second type of lesion and occurs in the pyloric mucosa Mann (1939) repeats his previous classification but suggests three types of ulcer instead of two the first—the acute ulcer the second—the anastomotic ulcer, and the third—the cinchophen ulcer which starts as a gastritis and involves both the fundic and the pyloric mucosa

According to Ivy (1946) one can state with confidence that there is only one type of ulcer which occurs in man the counterpart of which has been produced experimentally, and that this is the post-operative gastro-jejunal ulcer which is due primarily to acid acting on the jejunal mucosa which is more susceptible to acid than the gastric and duodenal mucosa

Leriche (1931) has pointed out that there is no difficulty in producing an ulcerative lesion but no method has produced ulcers which display the evolu tion of the disease in man The experimental ulcers are unassociated with hypersecretion and with hyperchlorhydria, experimentation has produced the lesion but not the disea e

Mann (1951) summarized the results of his investigations by stating that no effective method of treating the experimentally produced peptic ulcer has been discovered

It may be stated in conclusion that the experimental ulcer corresponds to the acute ulcer as seen in the human and that no experimental method has succeeded in reproducing in the ulcer bearing area the chronic lesion seen in man

The author s experiment which has so far only been attempted in the dog is based on theoretical considerations (*see* diagram p 276) its object is the production of reflux of bile into the stomach It is performed in two stages — a simple gastro-enterostomy followed after complete recovery of the animal by section of the duodenum below the entrance of the common bile-duct and suture of the open ends which are rejoined in continuity in order to prevent bursting of the stitches

The results of these experiments which are dependent on a time factor are not yet at hand

Moersch and Rivers, 1946, Grossman and Ivy, 1946, *Friesen, Baronofsky* and Wangensteen, 1946, Doran, 1947, Harkins and Hooker, 1947)

In criticising the relationship of the histamine ulcer to the ulcer in man it must be pointed out that unusually large doses of histamine were used, that is, 30 mg per day in dogs and 5 mg in guinea pigs, which are out of all proportion to the size of the animals and bear no relation to the amount of histamine used in man in whom 0 5 mg is sufficient to test the gastric response and 1 mg frequently produces unpleasant reactions

Caffeine-induced ulcer

Gross and microscopic erosions of the gastric mucosa were produced by the subcutaneous injection of an aqueous solution of caffeine sodium salicylate (Hanke, 1934a, b, Grasso, 1936, Molteni, 1938, Judd, 1943, Roth and Ivy, 1944a, b, c, 1945) Caffeine administered orally or intravenously to Pavlov and Heidenhain pouch dogs had no influence upon gastric secretion (Pincussohn, 1906, Bickel, 1910, Kestner and Warburg, 1923, Goldbloom, 1928, Petrowa and Ryss, 1930, Wichels, Brink and Lauber, 1933), it was found that decoctions of coffee and decaffeinated coffee stimulated gastric secretion when given by stomach tube to Pavlov pouch and duodenal fistula dogs (Pincussohn, 1906, Kestner and Warburg, 1923, Bickel and Eweyk, 1927, Farrell, 1928a) This discrepancy led to the observation that certain substances which had no secretory effect acquired stimulatory properties when roasted and that this change was due to the production of histamine (Eweyk and Tennenbaum, 1921, Bickel, 1929, Heupke, 1935, Bleyer, Demair, Fischler and Taufel 1936, Eichler, 1938) Merendino, Judd, Baronofsky, Litow, Lanning and Wangensteen (1941) found a marked rise in the gastric acidity and volume following the injection of 2,500 mg of caffeine alkaloid in beeswax *daily for four days (Ivy, 1944, Roth and Ivy, 1945)*

Giddings, Wynn and Haldi (1945) found that ulcers were produced in cats by caffeine only when the dose was large enough to kill the animal

CONCLUSIONS

According to Bolton (1913) the experimental lesions are primarily necrotic and not inflammatory After 48 hours the necrosed tissue disappears and leaves sharply punched-out ulcers with clean bases, exactly comparable in distribution and appearance to the acute gastric ulcers of infective origin in man Carlson (1923) stated that hyperchlorhydria does not occur in cases of experimental ulcer of the stomach and duodenum Morton (1927) pointed out the rapid healing of the experimental ulcer and the unaltered chemical characteristics of the gastric contents Mann (1935) emphasized that the type of ulceration produced remains acute, that there are usually more than one lesion which are shallow irregular erosions covering relatively large areas, which begin as a haemorrhage in the submucosa, and the ulceration of the mucosa appears secondarily to the vascular injury, the type of lesion is readily produced experimentally *by numerous methods and rarely, if ever,* becomes chronic The other type of lesion is produced by anastomosis of the

PART III

THE PRE-ULCERATIVE STAGE

Part I of this monograph dealt with the physiological considerations of the gastric function and the description of the responses of the gastro-duodenal tract to normal stimuli Part II dealt with the pathological considerations in order to provide the elements for the classification of the lesions This section deals with the intermediate stage between the two extremes in the evolution of the lesion and examines the pre ulcerative manifestations which correspond to the disorders of function before the structural defect has been finally established.

THE SIGNIFICANCE OF THE VARIATIONS OF THE GASTRIC SECRETIONS

There appears to be a great deal of confusion in relation to the role which hydrochloric acid assumes in the pathogenesis of ulcers The association of hyperchlorhydria with chronic ulcer must now be investigated in order to define the limits within which the fluctuations of the gastric secretions may be considered as normal before investigating their pathological variations

Spallanzani (1783) and Brown Séquard (1876) postulated that secretion of gastric juice is continuous Beaumont (1847) observed that free gastric juice was never found in the unstimulated stomach of Alexis St Martin Pavlov (1910) affirmed that the peptic glands remain at rest if they receive no direct or psychic stimuli Carlson (1916) stated that the gastric secretion was continuous Lim (1924) defined the basal secretion as the juice secreted by the stomach in the absence of all intentional and avoidable stimulation He found that the composition of the gastric juice whether basal or active, varies with the secretory rate, the quantity of juice increasing uniformly with the output of HCl The percentage increase is rapid at low secretion rates and relatively constant at higher rates The active differs from the basal juice in the quantity of fluid present at equal secretory rates The acid response to any stimulus varies directly with the basal secretory rate being the sum of the acid secreted at the initial basal rate and the acid evoked by the stimulus the latter being constant for the stimulus The fluid response is not constant and is the factor which may vary the character of the response to the different stimuli

NORMAL VARIATIONS OF GASTRIC ACIDITY

There appears to be no standard which indicates the range of the fluctuations of the normal gastric secretion

The resting juice

Butcher (1925–26) made the following observations on the fasting juice (50 estimations)

Quantity — Average 23 5 cc minimum 10 cc maximum 52 cc

Free HCl — Average acidity 3 2 cc minimum 0 0 cc maximum 20 cc N/10 HCl

On 32 occasions (72 per cent) there was no free HCl in the fasting juice and it was more often neutral when withdrawn immediately on rising than half an hour later

Imes (1935) measured the reaction of the isolated duodenum in dogs and found it to be alkaline with a pH which varied from 7 10 to 8 15 It was caused by weak alkalies or buffer substances which fluctuate quantitatively dependent on the relative proportion of pancreatic juice bile and duodenal secretion Hoerner (1935a, b) found in dogs that the reaction of the duodenal content in the fasting state ranged from pH 7 to 7 81 After a test meal it varied between 6 40 and 3 50 Following a carbohydrate meal it ranged from 6 75 to 4 26 and after a fat meal from 6 80 to 5 20 The acidity of the duodenum after meals appeared to depend largely on the rate and amount of acid formation in the stomach Draining of the pancreatic secretions to the outside of the body by pancreatic fistula caused *no* change in the reaction of the gastric content during fasting or after the various test meals used

According to Comfort (1945) the duodenal contents of healthy subjects with achlorhydria is alkaline during fasting in those with acid secreting stomachs it is acid both in the fasting state and after meals Rarely does the fasting duodenal content of a healthy subject whose stomach secretes acid in the more usual amounts become alkaline The acidity of the duodenal content after an Ewald or mixed meal is greater than in the fasting state

Rehfuss (1938) believed that nothing alters the acid response of an individual which is as characteristic of that individual as the nose on his face There is *no* evidence that the gastric glands under any conditions including pathological ones are able to secrete a juice of higher than normal acidity (Ihre 1939)

Breuhaus and Eyerley (1943) found that normal and ulcer patients had essentially the same fasting gastric pH values Histamine stimulation produced a lower gastric pH in normal than in ulcer patients As a rule anything which increased the flow of material from the stomach into the duodenum decreased the duodenal pH Food stimulates the duodenal secretion but does not increase its alkalinity in proportion to the acidity of the gastric content entering the duodenum The alternation of an antacid with milk and cream feeds raised the pH of the stomach the pylorus and the duodenum more than half hourly feeds alone

Hoelzel (1943) fasting on one day each week for 15 weeks found that the acidity and volume of the fasting gastric content are related to the degree of hydration of the organism Observations on his own gastric juice during the periods 1925–1929 and 1942–1944 (Hoelzel 1946) disclosed a slight decrease in acidity and about 50 per cent decrease in the volume of gastric secretion in the latter as compared with the former period

Janowitz Hollander Orringer Levy Winkelstein Kaufman and Margolin (1950) investigated the gastric response to three varieties of sham fed meals on 24 occasions in a female aged 24 years with oesophageal stenosis and a gastric fistula The magnitude of the response varied with the acceptability of the test meal Gruel evoked no response The maximum rate of secretion during the control periods of 15 m were 20 cc 1 56 m eq 3 200 pepsin units

Total acidity — Average 19 6, minimum 8 0, maximum 38 0 N/10 HCl

Mucus — This was constantly present

Bile — Bile was present on 9 occasions (18 per cent)

Pepsin — At 0 2 per cent HCl pepsin averaged 39 2 cc, minimum 14 0 cc, maximum 58 0 cc

Total chlorides — Average 96, minimum 66, maximum 139 (in terms of N/10 NaOH)

Rehfuss, Bergeim and Hawk (1914b) found that the quantity of fasting juice varied between 12–30 cc, while Carlson (1916) observed a variation of from 2 to 50 cc (40 cc average) per hour Hofstetter (1947) found that the intragastric *p*H *in situ* is 1–2 units higher than the *p*H of the juice *in vitro*, body temperature, filtration and stirring cannot explain the discrepancy

Secretory response to normal stimuli

Every individual has a characteristic form of gastric digestion (Rehfuss and Hawk, 1920) In normal individuals there are 3 forms of secretory response

(1) *In the hypersecretory type (40 per cent), the stomach is hypermotile* and gastric evacuation is rapid

(2) In the isosecretory type (30 per cent) the gastric motility is neither quick nor slow

(3) In the hyposecretory type (30 per cent) the stomach is hypomotile and gastric evacuation is slow

During the interdigestive period the secretory rate, both the free acidity and the total acidity are reduced (Rehfuss and Hawk, 1921)

Normally the outpouring of gastric secretion takes place only when stimulated by the ingestion of food, between meals the stomach remains empty or at the most contains but a few cubic centimetres of clear gastric juice showing perhaps a slight acidity (Galambos, 1926) Wide variations of acidity in the gastric content of both normal and diseased patients were found by Keefer and Bloomfield (1927) Distaste of food inhibits gastric secretion (Butcher, 1925–26)

Age and sex considerably influence the gastric secretions less gastric juice being secreted in advancing years Free gastric acidity appears to increase rapidly from childhood up to the age of 20 years when adult values are reached For man aged 20–40 years, free acidity ranges from 45 to 50 units which decrease to 30–35 units in the aged The values for women are somewhat lower and average 35 units in adults (Vanzant Alvarez, Eusterman Dunn and Berkson, 1932 Ruffin and Dick 1939)

There is a steady increase in the incidence of anacidity from youth to old age and it is higher in females than in males The incidence of anacidity in males averaged 10 7 per cent and in females 14 1 per cent (Polland, 1933) Rafsky and Weingarten (1947) found about 50 per cent of normal persons over 65 with 19 units or less of free HCl, 17 per cent had true achlorhydria

Hellebrandt and Brogden (1935) considered that the estimation of functional capacity in terms of the acidity response to a test meal or to histamine is not a valid procedure

individual in perfect health exhibited achlorhydria after 3 tests but showed free HCl in every sample, save the resting juice, of the fourth test meal Doig Motteram Weiden and Wood (1950) investigated 134 volunteers, 112 male and 22 female students aged 19–35 (average 24) years with the histamine test meal and found only one man with achlorhydria Gastric biopsy showed an unusual type of atrophy, no aetiological factor for gastritis was found but there was a family history of pernicious anaemia and hypochlorhydria on the maternal side

Gastric hyposecretion and achylia gastrica simplex have been described as congenital and possibly hereditary Cheney (1926) expressed the view that achlorhydria never occurs in the normal individual and that it may be a forerunner of several vital ailments Rehfuss (1929) believed that a careful study of achlorhydria would reveal some abnormality in the make up of the individuals Vanzant, Alvarez Eusterman Dunn and Berkson (1932) observed an increase of achlorhydria with increase in age While 4 per cent was found at the age of 20 years it gradually increased to 26 per cent at the age of 60 years females appeared to be more liable Bockus Bank and Willard (1932) observed much lower figures their average was 5 7 per cent compared with 12 1 per cent of Vanzant and her collaborators Their male cases contributed 4 8 per cent as compared with 10 8 per cent and their female cases 6 6 per cent as compared with 13 8 per cent They also observed that achlorhydria increases gradually with advancing years up to the age of 70 years Hartfall (1932) found that it was twice as common in females as in males In tropical climates gastric acidity appears to diminish Nye and Sippe (1932) reported an incidence of 18–20 per cent in Australia

Bloomfield and Polland (1933) suggested that anacidity may either be a normal variation of no pathological consequence or the direct result of an injury to the secreting cells or an involutional constitutional or abiotrophic phenomenon

Sagal, Marks and Kantor (1933–34) from a study of 6 679 cases with digestive symptoms (over a period of 12 years) concluded that age, next to constitutional predisposition appears to be the predominating factor in gastric acidity They pointed out that there is evidence to indicate that these acid levels (hyperchlorhydria in duodenal ulcer and achlorhydria in pernicious anaemia and cancer of the stomach) precede the development of the disease just as they persist after the cure It would appear that the degree of acidity—a constitutional factor—predisposes to a given disease rather than the disease producing a change in the acidity The presence of high acid values in old age may be considered as an index of longevity

Winkelstein (1942) found that in 5 583 cases 117 cases of true achlorhydria were encountered (2 2 per cent) Forty six cases were due to pernicious anaemia gastric carcinoma partial gastrectomy chronic gall bladder disease, Graves disease 69 cases were of undetermined aetiology (1 2 per cent)

Bockus (1943) observed a number of patients with hypochlorhydria initially which passed slowly through the various stages of more marked secretory deficiency until finally a permanent true achylia gastrica developed

PATHOLOGICAL VARIATIONS OF THE GASTRIC SECRETIONS

The normal daily variations of the gastric secretions vary considerably because they are directly dependent on a fluctuating number of stimuli, but each individual has his own pattern of secretion Normally an increase of stimuli will call forth an increase in the volume of gastric secretion, and a decrease of stimuli will result in a reduction of gastric secretion When, however, the normal stimuli produce a decrease in the response of the secretions, it is obvious that the capacity of the gland to secrete is impaired The permanent deviation of the secretions in one direction or the other must indicate the presence of a pathological condition

This deviation from the normal will be dealt with under two headings (1) hyposecretion, which is an inherent hereditary factor, with systemic repercussions and may be irreversible, and (2) hypersecretion, which is acquired and temporary, is a local reaction and is reversible

Hyposecretion

An absolute deficiency of hydrochloric acid is referred to as achlorhydria, while achylia is considered to indicate the complete absence of all gastric secretions but this is not strictly correct, since mucus and an aqueous fluid containing chloride are always secreted to a variable amount even in the most severe cases (Oliver and Wilkinson, 1933)

The fatal effect of total loss of gastric juice in dogs was shown by Dragstedt and Ellis (1930) who anastomosed the oesophagus to the duodenum with complete isolation of the stomach, with intact vagi and blood supply They observed that the total loss of gastric secretion from the body causes death in 5–8 days, that the continued loss of gastric juice from the body produces changes in the blood chemistry similar to those occurring after pyloric obstruction Failure of re absorption of gastric juice in the lower intestine is the chief cause of death in high intestinal and pyloric obstruction (Bottin 1938)

Achlorhydria in apparently normal individuals

It has been suggested that achlorhydria may occur in normal individuals and may have no pathological significance particularly as it is frequently symptomless Bennett and Ryle (1921) claimed 4 per cent of achlorhydria and 4 per cent of hyperchlorhydria in 100 normal medical students Baird, Campbell and Hern (1924a) who re examined 3 of Bennett and Ryle s students who showed complete absence of free hydrochloric acid at the first examination found that 2 had achlorhydria once but not when the meal was repeated, and that the third one could not be considered as showing normal health Lander and MacLagen (1934) examined 100 normal students between the ages of 18 and 32 by histamine test meals Only one

Achlorhydria and pernicious anaemia

Cahn and v Mering (1866) reported the finding of anacidity in a patient suffering from pernicious anaemia This observation has been generally confirmed

The familial relationship has been pointed out by Connor (1930) who found 25 9 per cent achlorhydria in 154 blood relatives of Addison s disease (42 3 per cent in those over the age of 40 years) Wilkinson and Brockbank (1930) collected (*a*) 125 families in which 2 or more members were affected with pernicious anaemia with or without the complication of combined degeneration of the cord, (*b*) 51 families in which pernicious anaemia and achlorhydria existed simultaneously, and (*c*) 14 families in which achlor hydria was found without pernicious anaemia and added 14 8 and 3 families to groups (*a*), (*b*) and (*c*) respectively

It has been generally inferred that the achlorhydria and the marked gastric hyposecretion which invariably accompanies pernicious anaemia are the result of a marked atrophy of the gastric mucosa

It appears that very occasionally there may be some free acid present in cases of pernicious anaemia, but it is generally accepted that achlorhydria precedes the onset of the disease sometimes by extremely long periods of time (Lichty 1907 Queckenstedt, 1913, Naegeli, 1917, Cobet and Morawitz 1920 Bie 1920 Hurst, 1923 Hunter 1923, Sturtevant 1925, Conner 1930 Davidson and Gulland, 1930, Moschkowitz 1931, Wilkinson 1932 Hartfall and Witts, 1933) The volume of fasting content is much smaller than normal it increases during remissions (Wilkinson 1932, Goldhamer 1937, Fouts Helmer and Zerfas 1937)

Many cases reported as pernicious anaemia with the presence of acid were erroneous and misleading (Askey, 1944, Wintrobe, 1946)

Aetiology of achlorhydria

Several hypotheses have been advanced to explain the variations of gastric acidity in childhood and young adulthood It has been suggested that achlorhydria is secondary to chronic gastritis of exogenous origin and that it follows particularly after acute fevers through the destruction of the acid secreting cells by an inflammatory process, that it is of neurogenic origin because of the presence of functional nervous symptoms in a large proportion of cases, and that it is attributable to abiotrophic changes in the acid secreting cells which appear after birth The most important suggestion is that it is due to a constitutional abnormality as shown by its familial and hereditary incidence

Faber (1926) pointed to the existence of an inherited or familial factor in some patients with gastritis, believing that this factor renders the stomach more susceptible to irritants and that gastritis and secondary achlorhydria may occur more readily in such families Hurst (1934) thought that gastritis and constitutional factors were of equal importance

Moutier (1935) as a conclusion to his review of gastritis emphasized that

Hypochlorhydria and achlorhydria in children

Brüning (1920), in Germany, made 300 examinations with an Ewald Boas test-meal in children aged 2–15 years For the ages of 2–10 years before the first World War, total acidity was 55 6 and free acidity 108 as compared with 42 5 and 11 7 during the war, for the ages 10–15 years, 63 6, 23 6, 48 7 and 18 respectively Twenty seven per cent had no gastric symptoms while the remaining 73 per cent had some dyspeptic symptoms Sixty three cases (21 1 per cent) were hypochlorhydric or achlorhydric Chievitz (1921) who examined 53 infants with a sweet barley water test meal found no case of achlorhydria Sauer, Minsk and Alexander (1922) found in children, aged 7–11 years, with good appetite, that the average gastric emptying time was 4½ hours and in children with poor appetite more than 6 hours The average total hydrochloric acid for the first group (12 children) was 61 2 ,with free hydrochloric acid 26 3 and for the second group (21 children) 49 4 and 14 9 respectively Bloch (1923) found a lowered gastric secretion in more than 50 per cent of his cases with intestinal lesions, and 25 per cent of the infants had a complete achylia which persisted for periods of several weeks up to 11 months Similar observations were made by Hertz (1921) Klementson (1924) reported observations on 166 children aged 1–12 years The secretion of hydrochloric acid was found to be considerably lower than that in adults The lowest secretion was found at 1 year, with gradual increase up to the period of 4–7 years and with little change from 7–12 years Ylppo (1924) found that a reduction in the amount of hydrochloric acid occurred in children whose temperatures were raised both artificially, by immersion in hot water, and by infection From an examination of normal infants David sohn (1921), Marriott and Davidson (1923), Babbott Johnson, Haskins and Shol (1923) and Davidson (1925) found that gastric samples withdrawn at the height of digestion usually showed a value of from *p*H 3 to *p*H 5, few cases falling below *p*H 3, but there was an increased acid production with increased age Wright (1924) found that in children aged 6–15 years the free hydrochloric acid and the total acidity is apparently the same as in adults Absence of hydrochloric acid was observed in 4 out of 250 cases in one of whom there was a small amount present and in another no free hydrochloric acid one year later Katsch (1926) saw only a few cases and Bunce (1929) gives a figure of 1 5 per cent Copeman and Hill (1929) noted 7 with achlorhydria in 66 children (10 6 per cent) aged 8–16 years who were convalescent from rheumatic heart disease or surgical tuberculosis Parsons (1929) observed 10 of 51 cases with no free acid which showed acid on a different test meal, while Bray (1930) found less than 10 per cent amongst normal children Dietrich and Shelby (1931) found that the figures obtained for free hydrochloric acid and total acidity of the gastric secretion of healthy children presented wide variations and that a normal figure could not be stated Miller (1941) considered that the gastric acidity of an infant at birth may bear a close similarity to that of the mother

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pouches are stimulated by repeated injections of histamine They also found the same result from the intravenous injection of gastric mucin but not from pepsin Hebbel and Gaviser (1949) found achlorhydria in 65 per cent of 284 cases resected for gastric carcinoma

Achlorhydria in association with general disease

A great variety of diseases other than carcinoma of the stomach and pernicious anaemia are associated with low gastric secretions

Oliver and Wilkinson (1933) found that, combining both sexes the occurrence of achlorhydria in general disease other than artificially produced gastric anacidity appears to be in the order of 10 to 15 per cent

Anacidity in cancer other than cancer of the stomach was reported in 60 per cent of 15 cases by Moore Alexander, Kelly and Roaf (1905) in 22 4 per cent of 65 cases by Keefer and Bloomfield (1926) and 14 of 38 by Friedenwald and Brown (1931)

Niazi State Trelcar and Wangensteen (1949) found that of 1 315 patients over the age of 50 years 244 had malignant extragastric lesions 32 8 per cent had achlorhydria (after histamine stimulation) and 24 6 per cent had hypochlorhydria in 93 patients with benign extragastric tumours 30 per cent had achlorhydria and 28 per cent had hypochlorhydria Of 906 patients with non neoplastic diseases 36 per cent had achlorhydria and 33 per cent had hypochlorhydria of 57 patients with gastric carcinoma 85 per cent had achlorhydria and 5 per cent had hypochlorhydria of 13 patients with gastric polyps 100 per cent had achlorhydria

Achlorhydria in association with allergic diseases had been reported by Duke (1925) Maxwell (1925) Criep and MacElroy (1928) and Rowe (1931, 1932) Bray (1930–1931) found in asthmatic children aged 6 months to 10 years that 12 per cent had no hydrochloric acid

The association of anacidity with *chronic arthritis* was reported by Borries (1910) Mackenzie and Wallis (1912), Faber (1913) Coates and Gordon (1923), Keifer and Bloomfield (1926b) Miller and Smith (1927) Wilkinson and Oliver (1931)

The association of achlorhydria with diseases of the endocrine system has been observed by Sturgis (1922), for myxoedema by Lockwood (1925) and Brown (1930) for hypothyroidism hypothyroidism with hypopituitarism by Moll and Scott (1927), Lerman and Means (1932) Berryhill and Williams (1932), and Meulengracht (1932) for exophthalmic goitre and myxoedema

The association of achlorhydria with deficiency diseases appears to be of considerable significance It has been reported according to Oliver and Wilkinson (1933) in pellagra by Johnson (1911) Myers and Fine (1913), Givens (1918) Guthrie (1926) Bunce (1929) Boggs and Padget (1932), in beriberi by Kitamura and Shimazono (1913) in tropical sprue by Baumgartner and Smith (1927) and in a typical sprue by Reed and Ash (1927) in vitamin A deficiency by Pilat and Chang (1932) in diabetes mellitus by Wiechmann and Elzas (1929) Wohl (1931) Rabinowitsch Fowler and

the gastric secretions play a considerable part in general equilibrium of the body

Shay, Gershon Cohen and Fels (1941) reject the view of Bloomfield and Polland (1933) that the lack of gastric acid is an involutional phenomenon of no special clinical significance, they emphasize that it plays an important role in gastro intestinal motility, in calcium, iron and vitamin absorption, in thyroid disease and diabetes, and that pernicious anaemia is invariably associated with its absence

Kruger (1943) *studied 325 patients in various stages of pulmonary tuber*culosis and found that as the degree of the disease progressed, the incidence of gastric anacidity increased Significant fever caused an increase in incidence of achlorhydria Anaemia *per se* did not affect the degree of acidity

Biopsies taken by the flexible gastroscope by Wood, Doig, Motteram, Weiden and Moore (1949) in 18 patients with severe atrophy (gastric ulcer and carcinoma excluded) showed achlorhydria with a low total volume and low or absent pepsin In the presence of a normal or nearly normal mucosa the secretion was nearly normal or 'intermediate

Achlorhydria and carcinoma

The frequency of achlorhydria in gastric cancer is well established

Brunschwig and Clarke (1939) state that approximately 60 per cent of patients with carcinoma of the stomach exhibit achlorhydria In a study based upon some 70 specimens of cancerous stomachs removed at operation or necropsy, no correlation was possible between the site of the neoplasm, its size and histological type on the one hand, and the quality of gastric secretion as observed following the histamine test, on the other hand Because of the rather frequent observation that achlorhydria existed in a cancerous stomach of patients in whom the microscopical appearance of the fundic mucosa was not markedly altered, Brunschwig, Schmitz and Rasmussen (1940) tested experimentally the hypothesis that such achlorhydria might be the result of a local preponderance of a gastric secretory depressant Two categories of test substances were employed (1) boiling 0 2 per cent *HCl* extracts of cancerous and control stomachs and tissues, and (2) the juices from cancerous and control stomachs They concluded (*a*) that the achlorhydria of cancerous stomachs is associated with a local concentration of a gastric secretory depressant which is demonstrated in extracts of achlorhydric cancerous stomachs and juices from such stomachs and (*b*) that the gastric secretory depressant was also observed in achlorhydric juices from patients with pernicious anaemia in incidence equal to that observed in achlorhydric juices from cancerous stomachs They were unable to establish the nature of the depressant

Blackburn and Code (1948) confirmed the observations of Brunschwig and his co-workers that there is an inhibitor in achlorhydric gastric juices of patients who have pernicious anaemia, and also that it is present in achlorhydric gastric juice from patients without other demonstrable changes in gastric function The gastric secretory inhibitor present in the gastric juice of man also inhibits the secretion of Heidenhain pouches in dogs when these

0 3 per cent and 0 016 per cent respectively in gastric ulcer close to the pylorus 0 3 per cent 0 016 per cent respectively, and the protein HCl 0 082 per cent, in gastric ulcers located in the middle of the stomach the total acidity was 0 321 per cent, the free acidity 0 01 per cent and the protein HCl 0 0824 per cent

Boldyreff (1915) has shown that where almost pure normal gastric juice was obtainable from man the acidity was from 0 35 to 0 48 per cent of HCl Carlson (1915a) has shown that normally in man the appetite juice has an average acidity of 0 45 per cent and may reach a total acidity of 0 55 per cent without showing any of the so-called symptoms of hyperacidity This observation was confirmed by Hardt (1916)

The association of hyperchlorhydria with ulcer was observed by many authors Cheney and Bloomfield (1927–28), in 17 gastric and 20 duodenal ulcer patients found gastric acidity and the volume of gastric secretion to be greater than in people without gastric disease

Polland (1933) found that in 130 cases of duodenal ulcer 91 3 per cent of the subjects had a total acidity and 79 2 per cent had volumes of secretion higher than the mean values of normal persons of the same age and sex In 36 cases of gastric ulcer 91 7 per cent of the patients had a total acidity and 75 per cent had volumes of secretion higher than the mean values of normal people of the same age and sex Vanzant Alvarez Berkson and Eusterman (1933) observed that the curve representing gastric secretion in cases of ulcer was found to be parallel to that representing secretion in normal persons but shifted upwards a distance corresponding to about 12 units while in gastric ulcer the acidity was reduced by 5 4 units in men and 6 6 units in women Ulcer near the pylorus produced no variation from the normal ulcer in the middle third of the stomach produced a reduction of 4 8 units while ulcer in the upper third of the stomach reduced it by 7 9 units Ulcer near the pylorus increased the volume by 35 5 cc those in the middle third by 20 4 cc and those in the upper third had no effect Brown and Dolkart (1937) observed that there was no significant trend in the gastric acidity prior to recurrence of activity of an ulcer In the same patient the level for free acid may rise fall or undergo no significant change before recurrence

According to Ihre (1939, 1947) hypersecretion is present chiefly in chronic duodenal ulcer, but also in chronic gastric ulcer Kearny Comfort and Osterberg (1941) found a rough parallelism between the degree of gastric secretory activity and the *p*H values of the duodenal content in normal persons but the same parallelism could not be demonstrated satisfactorily in subjects with duodenal ulcer *The duodenal mucosa of patients with duodenal ulcer* was bathed in a more highly acid fluid for longer periods than in normal persons Schiffrin and Ivy (1942) observed that acid values higher than those usually found in normal subjects were common in the presence of ulcer particularly duodenal ulcer

Hypersecretion of the interdigestive phase has been observed with duodenal ulcer (Dragstedt and Vaughn 1924) Brown and Rivers (1945) and Ihre (1947) found that male patients have much higher values than the female

Watson (1931) and Root (1931), in cardiovascular disease by Hufler (1889), Leist and Weltmann (1921), Friedenwald and Morrison (1928), and Robbins (1929), and in renal disease by Biernacki (1889), Leist and Weltmann (1921) and McEnery, Myer and Ivy (1927), in disease of the lung by Brieger (1889), Perla (1926), Brooke (1928), Torning (1929) Guido (quoted by Faber, 1935) found that 26 per cent of his malarial patients had an achlorhydria which frequently persisted throughout life

The association of achlorhydria with skin diseases particularly in acne rosacea, was reported by Ryle and Barber (1920), by Brown (1925) and Rulison (1927), by Ayres (1929) in psoriasis, by Neugebauer (1914) in secondary syphilis and by Eusterman (1931) in gastric syphilis

The frequent occurrence of microcytic anaemia among patients with achlorhydria, whether congenital or hereditary, or secondary to gastritis injury or gastric surgery is so striking that it assumes aetiological significance, the achlorhydria being present before the anaemia (Meulengracht, 1932, Hurst, 1932, Hartfall and Witts, 1933, Oliver and Wilkinson, 1933)

Wilkinson and Brockbank (1930) found in the course of their investigations of the familial tendency that microcytic anaemia was quite commonly present in other members of the families, many with achlorhydria They suggested that the conversion to pernicious anaemia is open to serious consideration in such individuals Monaghan, Bockus, Kornblum and Moffit (1936) believed that hypochromic, microcytic anaemia which responds to iron therapy may be conditioned primarily by gastritis since the anaemia is often found in the absence of achlorhydria Oliver and Wilkinson (1933) fully confirm the findings of other observers that achylia gastrica occurs in 100 per cent of cases of subacute combined degeneration of the spinal cord

Mann and Mann (1939) found that transitory achlorhydria to histamine may be produced in dogs by exposure of gastric mucosa to dilute solutions of mercuric or cupric salts no effect was noted using salts of lead, manganese or zinc in much greater concentrations

Hypersecretion

The association of hypersecretion with peptic ulcer

There is much evidence to show that there is only one pathological manifestation which is invariably associated with hypersecretion namely chronic peptic ulcer or its pre ulcerative stage Strictly, it is hypersecretion which is meant and not hyperchlorhydria—the term which is generally used—since the acidity of the hydrochloric acid does not exceed the maximum of 0 5 per cent Christiansen (1911) and Michaelis and Davidson (1910–11) determined the acidity of the gastric content in cases of dyspepsia gastric cancer, gastric ulcer and many other pathological cases They found considerable variation in the acidity but in no instance did it exceed 0 43 per cent

Patterson (1914) gave the following four analyses of gastric contents

In duodenal ulcer distal to the pylorus, the total acidity was 0 32 per cent and the free acidity 0 02 per cent, in duodenal ulcer close to the pylorus

Sandweiss, Sugarman, Podolsky and Friedman (1946a, b), Sandweiss, Friedman Sugarman and Podolsky (1946), studied 38 normal persons (73 studies) and 29 patients with duodenal ulcer (77 studies) with particular attention to hypersecretion and hyperacidity and their bearings on the management of patients with duodenal ulcer They concluded that both normal persons and patients with duodenal ulcer secrete gastric juice during the night even when the 6 p m meal consists of foods usually allowed ulcer patients Following a fairly well balanced meal at 6 p m (which included beef broth and fish) the nocturnal gastric juice from patients with duodenal ulcer is approximately of the same hydrochloric acid concentration and volume (obtained by continuous suction) as is the gastric juice from normal subjects of the same sex

Voegtlin (1947) found that the mean nocturnal gastric acidity in patients did not show a tendency to decrease as healing proceeded Levin, Kirsner and Palmer (1948b) observed that in the same patient with duodenal ulcer the 12 hour nocturnal gastric secretion is usually unaltered with healing of the ulcer The average 12 hour nocturnal gastric secretion of patients with active ulcer is not significantly different from patients with healed duodenal ulcer but 12 hour nocturnal gastric secretion in patients with healed duode nal ulcer and who are without symptoms is significantly greater than that of normal healthy individuals Levin Kirsner Palmer and Butler (1948a) ob served wide variations in the continuous nocturnal gastric secretion from one individual to another and considerable spontaneous variation was noted in the same person which occurred from hour to hour The volume and output of hydrochloric acid were significantly higher in the first six hours of the night than in the last They found that the average volume of secretion in patients with duodenal ulcer is approximately twice that of the normals and the output of free hydrochloric acid approximately three and a half times as great They explain the reason for disagreement with figures given by Sandweiss as being due to a different method in the collection of samples

According to James and Pickering (1949) night secretion in gastric ulcer is more or less similar to normal secretion One of the striking features was the tendency for the gastric contents to approach neutrality in the early morning

Breuhaus Akre and Eyerly (1950) found that the rate of secretion was usually greater before than after midnight in both normal and duodenal ulcer cases An increased volume of night secretion was found after treatment with calcium carbonate tribasic calcium and magnesium phosphate during the day in ulcer patients

Olson and Bridgewater (1954) investigated the question whether an ulcer patient secretes more gastric juice than a normal person Twelve hour noctur nal gastric secretion studies showed that normal men in a penitentiary secrete a larger volume and more acid than normal subjects as reported by other observers Comparison of the 12 hour night secretion of normal subjects and of duodenal ulcer patients showed no significant difference in volume and acidity and the gastric secretory response to the Hollander insulin test

patients for free hydrochloric acid and total acidity Musick, Avey, Hopps and Hellbaum (1946) observed in patients with duodenal ulcer during remission that the total amount of free HCl increased from 363 mg to 631 mg (an increase of 174 per cent), and in active duodenal ulcer to 957 mg (an increase of 264 per cent)

Doll, Jones and MacLagan (1949) concluded that hypersecretion of gastric juice precedes the formation of peptic ulcer Ivy, Grossman and Bachrach (1950) believed that hypersecretion precedes the ulcer and persists after the ulcer has healed Erb (1950)observed a patient with marked acidity without peptic ulcer but with hypertrophy of Brünner's glands who promptly developed a peptic ulcer after duodenal resection Patients with duodenal ulcer secrete as much acid during asymptomatic intervals as they do during exacerbations (Littman, Rosiere and Ivy, 1950, Grossman, 1951)

Night secretion in relation to the ulcer problem

Much attention has been given to claims that the excessive continued night secretion constitutes the main difficulty of the ulcer problem (Sippy, 1915) Normally the night secretion is slight although continuous (Chalfen, 1928) and generally neutral in reaction, the waking state producing a prompt elevation of the acid level Galambos (1926) has emphasized that when the stomach is empty no secretion takes place and that during the night s rest gastric secretion is relatively inhibited so that often the amount found in the stomach in the morning will be relatively much less than one would expect to find in comparison to the height of secretion during a test meal Henning and Norpoth (1933) found no acid secretion during the night in the normal but high acid values in patients with peptic ulcer Winkelstein (1935) found the average acidity in 62 patients with duodenal ulcer markedly higher than in 20 controls Similar observations were made by Hellebrandt, Tepper, Grant and Catherwood (1936) Wangensteen Varco Hay, Walpole and Trach (1940), Mears (1943), Cornell, Winkelstein and Hollander (1944), and Dragstedt, Palmer, Schafer and Hodges (1944)

Sandweiss, Sugarman and Friedman (1941), who examined the gastric secretion during the night in normal individuals and peptic ulcer patients, found that (1) in both normal individuals and ulcer patients, two peaks in concentration of free acid usually occurred one peak, between 11 p m and 1 a m , the other between 3 a m and 5 a m , after 5 a m both the volume of secretion and the concentration of free acid were usually very greatly reduced, the juice often showing no free acid (2) the volume of secretion was significantly higher in the ulcer patients as compared with the normal individuals, though the concentrations of free acid in the two groups were approximately the same (3) bile was frequently present, usually after midnight Mucus was often found, particularly towards the morning hours, (4) in both the normal individuals and the ulcer patients the volumes secreted were much higher than reported This increase in volume may be explained by the fact that they used beef extract and fish in their meals—foods known to be strong stimulants of gastric secretion

Various causes have been suggested to explain the increase of the gastric secretions

Ewald (1893) considered hyperchlorhydria as a neurosis of the stomach He emphasized that one must distinguish between catarrh, that is to say a chronically inflamed condition of the glandular layer of the stomach and a direct or indirect nervous irritation Inflammatory states reduce the acid secretions and promote the alkaline secretions However the opposite view was held by Dujardin Beaumetz (1881), Korczynski and Jaworski (1891) and Hayem (1892) Lim (1924) stated that hypersecretion of juice, apart from acid may occur from an increase of the non acid bearing fluid Considering that the relation of the stimulus to response is constant the degree of the secretory state must depend on the intensity of stimulation hence hypersecretion of acid may be translated to mean hyperstimulation

According to Galambos (1926) two types of gastric secretion may be distinguished that of the normal stomach and that of the stomach affected with irritative secretory disturbance The introduction of a Rehfuss tube in the normal stomach after fasting produces no gastric secretion either by drainage or suction, while in the stomach affected by irritative secretory disturbance there is hypersecretion on fasting usually with hyperacidity Bolton (1928) and MacLagen (1934) believed that hyperacidity is due to interference with pyloric relaxation

According to Hunt (1947) there appears to be no generally accepted explanation of the gastric hypersecretion which is frequently associated with duodenal ulcer, and on simple theoretical grounds it seems that three hypotheses must be considered (1) that the humoral stimulating mechanism is hyper active (2) that the nervous stimulating mechanism is hyperactive, and (3) that the glands of the stomach are hyper responsive He argued that if the gastric hypersecretion associated with duodenal ulcers were due to a hyper reactive stomach, it might be expected that in such cases histamine, which excites the secretory mechanism even in the absence of the extrinsic nerve supply would give rise to an exaggerated secretory response as compared with that of normal subjects On the other hand, if the cephalic centre were hypersensitive it might be expected that the gastric secretory response to a fall in blood sugar after the intravenous injection of insulin would be greater in patients with duodenal ulcers than in normal subjects The published figures of Ihre (1939) who performed successive histamine and insulin tests on normal subjects and patients with gastric and duodenal ulcers allow these two hypotheses to be tested without further experimental work Hunt therefore examined the statistical figures presented by Ihre and found that the secretion of chloride in response to histamine stimulation was of the same order in normal subjects and patients with gastric ulcers The patients with duodenal ulcers secreted a mean of 54 per cent (standard error of mean 15 per cent) more than the normal group This difference is significant since it is more than three times its own standard error The cases of duodenal ulcer secreted a mean of 56 per cent (standard error of mean 15 per cent) more pepsin than the normal group in response to histamine Hunt therefore con

showed no significant difference between normal and ulcer patients

Atkinson and Henley (1955) investigated simultaneously by double lumen tube the contents of the stomach and the first part of the duodenum, they found that in gastric ulcer cases, duodenal ulcer cases and controls there was a fall in acidity during the night

Fasting juice in duodenal ulcer

Ryle (1926) has drawn attention to the tendency towards higher values in the fasting juice with duodenal ulcer Bockus, Glassmire and Bank (1931) found that it was almost twice that of the average fasting acidity in a large series of normal persons Bloomfield, Chen and French (1940) found wide variations in the basal secretory controls which, to a large extent, were wiped out by histamine stimulation Duodenal ulcer cases often exceeded the highest control values but the values in gastric ulcer cases were similar to the controls Comfort and Osterberg (1945) found that the fasting contents of the duodenum in cases of duodenal ulcer are similar to those of normal persons, both in the fasting state and after meals

Levin, Kirsner and Palmer (1950) found that the volume and free hydro chloric acid content of the fasting (basal) secretion in patients with duodenal ulcer is significantly greater than that of normal healthy individuals

Variations in the secretion of pepsin in relation to peptic ulcer

Polland and Bloomfield (1930–31) found that the histamine stimulated pepsin output of ulcer patients fell within the same range as the controls Estimation of the secretion of pepsin carried out in cases of duodenal ulcer and pseudo ulcer by Vanzant, Alvarez, Berkson and Eusterman (1933) confirmed the observation (Osterberg and Vanzant, 1932, Vanzant, Oster berg Alvarez and Rivers, 1933) that values for pepsin are usually increased in the presence of peptic ulcer and the high degree of correlation between the amount of the ferment and the severity and intractability of the symptoms

Mullins and Flood (1935) found that the average peptic activity of the fasting residuum in 7 ulcer patients was approximately the same as that in a miscellaneous group Helmer and Fouts (1937) observed that in patients with peptic ulcer, as well as in nervous individuals the pepsin concentration of the histamine stimulated gastric juice was 2–4 times as high as in the normal Ihre (1938) found the same average concentration of pepsin for both normal and duodenal ulcer patients Ivy, Grossman and Bachrach (1950) consider that the pepsin concentration does not have any aetiological significance

Causes of hyperchlorhydria and hypersecretion

The term hyperchlorhydria implies an increase above the normal in the concentration of the hydrochloric acid of the gastric juice which can be neutralized by N/10 NaOH, while the term hypersecretion implies an increase of the volume of the gastric juice

THE INFLAMMATORY REACTION OF THE GASTRIC MUCOUS MEMBRANE

INFLAMMATION—ITS SIGNIFICANCE IN RELATION TO THE PEPTIC ULCER PROBLEM

Many theories have been put forward to explain the mechanics of the inflammatory process It may be of interest to give a brief historical summary of the views which have been suggested to explain a phenomenon which is of fundamental importance in the pathogenesis of chronic peptic ulcer

Hippocrates (circa 400 B C) thought that the local irritation drew towards the lesion an exaggerated flow of blood and humour— ubi stimulus ibi fluxus —and that the raising of the temperature on the surface of the affected organ would destroy and remove the cause of the irritation Celsus (1st century) enunciated the famous aphorism notae vero inflammationis sunt quatuor rubor et tumor cum calore et dolore —the four cardinal signs of inflammation are redness, swelling heat and pain Galen (circa 200 A D) who added functio laesa — a local deranged function thought that the blood of the veins became hotter and according to Sydenham (17th century) it also acquired effervescence and produced inflammation when it reached the tissues Boerhaave (early 18th century) thought that the blood in the distended vessels and capillaries was stagnant before getting overheated

John Hunter (1794) observed that the temperature of the inflamed tissues did not exceed that of the splanchnic organs that the dilated blood vessels allowed for an easier supply of blood which produced an active congestion as opposed to passive congestion or stasis and that its purpose was to restore the parts to their natural function Rokitansky (1842) suggested that the stasis was followed by exudation Virchow (1852) identified inflammation with burning and destruction and the inflammatory reaction as a degenerative manifestation (inflammatio febris localis) Cohnheim (1889) introduced the element of diapedesis

Metchnikoff (1892) attempted to establish a biological theory of the process as an adaptation of the organism to its environment He suggested that inflammation was a salutary defence reaction of the organism against irritants The phagocytes—microphages and macrophages now generally referred to as polymorphonuclear leucocytes and mononuclear cells—migrate to the infected area and surround destroy and absorb the bacteria by intracellular digestion Adami (1909) Herxheimer (1919), Marchand (1921) and Thoma (1922) held similar views Wright (1904) added to Metchnikoff s concept the action of opsonins Lubarsch (1898 1921, 1923 1928) distinguished the degenerative or alterative the exudative or infiltrative and the proliferative types of inflammation

cluded that there is no significant difference between the activity of the vagal centres in the three groups as revealed by the figures for chloride or pepsin and that the peripheral secretory mechanism is hyper reactive in those cases of duodenal ulcer showing gastric hypersecretion

Hunt (1950) analysed the secretory responses of the stomach to histamine and insulin in normal people and in patients with peptic ulcers after the secretions had been divided theoretically into two hypothetical components containing the inorganic ions and pepsin, supernormal secretion of acid and alkaline components and pepsin by patients with duodenal ulcer can be entirely explained by their increased peripheral secretory reactivity, the supernormal secretion of the alkaline component by patients with gastric ulcer can be explained partly by an increased peripheral reactivity and partly by an over active central mechanism

increase in the permeability of the capillary walls and migration of leucocytes toward the site of the stimulation The result will be an initial increase in blood flow throughout the area followed by a gradual slowing down of the circulation at its centre associated with the clumping of blood-cells and the formation of microthrombi At the height of inflammation increased arterial flow and capillary stasis will coexist in what Ricker (1924) called peri staltic hyperaemia Ungar concluded that from an objective biological point of view inflammation is the result of a complex chain of biochemical reactions controlled by the endocrine system Since inflammation is the normal response of animal tissues to environmental changes it definitely has some survival value It seems however that when the same sequence of biochemical reactions occurs at the systemic level, instead of being limited to a tissue the resulting response termed the shock syndrome (Moon 1938) is undoubtedly purposeless and harmful This seems to suggest that the same mechanism can have adaptive value at a local level and no homeostatic significance whatever when it operates at the level of the organism as a whole

GASTRITIS

The term gastritis has given rise to much confusion While the suffix itis denotes an inflammatory condition and is applicable to the acute variety it cannot be applied as a general term to the chronic variety because its use has not been restricted to the inflammatory reactions of the gastric mucous membrane but has also included conditions which no longer show, or may never have shown, any form of inflammatory reaction Card (1941) pointed out that if the term chronic gastritis means any increased cellular infiltration of the mucous membrane then nearly everyone over the age of 40 years is suffering from gastritis

According to Bergmann and Katsch (1927) gastritis is an anatomical conception and they suggested that in clinical cases in which there is no evidence of inflammation it should be called gastrosis Warren and Meissner (1944) stated that considerable misunderstanding has arisen because the term chronic gastritis means many things to many men To the clinician it means disturbance of gastric function of a non specific type To the gastroscopist it means changes in colour and shape of the mucosal folds To the pathologist it has meant acute or chronic exudative inflammation Too often a pathologist has centred his attention on the exudative portion of the gastritis and has overlooked the epithelial changes Chronic gastritis is a labile condition which may regress and which need not necessarily progress

Chronic gastritis may be said to represent one of two conditions which are strikingly differentiated from each other, it may be associated either with (*a*) a hyperactivity of the motor and secretory functions of the stomach that is to say the hypertrophic type or with (*b*) a hypoactivity of the motor and secretory functions of the stomach—the hypotrophic or atrophic type

Classification of Gastritis

Clinically gastritis may be classified according to whether it is an acute or a chronic manifestation

Aschoff (1922) interpreted inflammation *clinically* as rubor, tumor, calor, dolor, *morphologically* as degeneration, exudation, proliferation, *physiologically* as circulatory disorders and local immunity reactions He suggested as *aetiological* the infectious toxic or traumatic (circulatory) causes, and as a *functional* definition *defensio, reparatio, regeneratio*

The similarity between the manifestations of inflammation and the response to injections of histamine suggested that histamine or an "H" substance is liberated by injury of the tissues which produces vascular reaction and increased permeability (Lewis and Grant, 1924)

Roussy, Leroux and Oberling (1929) pointed out that the inflammation involves all the elements in the tissues, the cells, the intercellular substances, the blood vessels and the nerves Tzanck (1932) considered that the pheno mena of immunity and anaphylactic intolerance are closely related to inflammation (antiboby formation with fever and leucocytosis) The vascular features of inflammation, systemic leucocytosis, the migration of leucocytes into the area of injury, the initiation of repair and the cessation of cellular proliferation are each explainable as self initiated, locally controlled physiological responses which are independent of innervation (Moon 1938)

According to Menkin (1940) inflammation may be defined broadly as the complex vascular, lymphatic and local tissue reaction elicited in higher mammals by the presence of micro organisms or of non viable irritants It represents a basic or elemental reaction to injury whereby the deleterious agent tends to be localized and ultimately destroyed The inflammatory reaction may be truly regarded as an immunological mechanism of definite significance Menkin recovered a crystalline nitrogenous substance (leukotaxine) from inflammatory exudates which induces in cutaneous tissue a rapid migration of polymorphonuclear cells through the endothelial wall of the small vessel The inflammatory reaction is initiated by the derangement in local fluid exchange It subsequently proceeds through a series of inter dependent sequences which ultimately tend to localize and dispose of the irritant An inflamed area can be considered as shunted off from the rest of the organism It has its own metabolism, its own hydrogen ion concentration and its own modified circulation and ultimately leads to organization and repair of the affected tissue

Lumiere (1949) who observed that a filtered extract of red blood corpus cles precipitates the serum of the same subject, believed that the problem can be resolved by the theory of colloids He suggested that precipitation or floculation produces insoluble foreign bodies which are removed by intra protoplasmic digestion or by diapedesis and that it is easy to produce inflammation at any given point by injecting aseptic particles which are responsible for the leucocytic infiltration

Ungar (1952) who described the pattern of inflammation stated that, when an environmental change whether physical (mechanical trauma, tempera ture, radiation), chemical ('irritant' substances), or biological (bacterial infection toxin, venom antigen antibody reaction), stimulates or injures a tissue, the following reaction will develop dilatation of the blood vessels,

other Inflammatory gastritis is a lesion characterized in its acute stage by the presence of erosions exudate in the gastric pits activity of the surface epithelium destruction of glands and polymorphonuclear infiltration of the mucosa accompanied by transmigration of the surface epithelium by polymorphonuclear leucocytes In its chronic state it is characterized by atrophy of the glandular parenchyma fibrosis of the mucosa and submucosa intense infiltration of the interstitial tissue by plasma cells and lymphocytes and metaplasia of gastric to intestinal epithelium Non inflammatory gastritis or idiopathic atrophy of the stomach is characterized by extreme atrophy of all coats of the stomach wall and is not accompanied by any evidence of past or present inflammation

Maimon and Palmer (1946) suggested that superficial and hypertrophic gastritis may be variations of the same process rather than separate and distinct entities Schindler (1947) distinguished between the chronic superficial atrophic and the chronic hypertrophic gastritis The appearance of the intestinal type of epithelium (goblet and Paneth cells) in the stomach indicates the presence of long standing inflammation (Williams 1950 Arey and Bothe 1950) Magnus (1952) suggested the following classification (1) acute erosive gastritis, (2) endocrine or genetic in origin (3) chronic gastritis

Stempien Oritt and Karr (1953) observed endoscopically the following zonal distribution of gastritis

Superficial gastritis	
The anterior wall body was affected in	50 per cent
The antrum and body diffusely in	37
Atrophic gastritis	
The antrum and body diffusely in	75
The anterior wall body in	23
Hypertrophic gastritis	
The posterior wall body in	42
The body diffusely in	17
The antrum and body diffusely in	3
Mixed gastritis	
(1) Hypertrophic—posterior wall / atrophic—anterior wall } in	60
(2) Hypertrophic—body / atrophic—antrum } in	40

Giant hypertrophic gastritis

Stoerk (1922) described the état mamelone as a true hypertrophy of the gastric mucous membrane, but did not consider it as an actual gastritis an opinion confirmed by Steinberg (1927) Palmer (1949) considered that giant hypertrophic gastritis is a variant of chronic hypertrophic gastritis and represents the ultimate in the severity of surface changes in this disease where nodulation and pseudopolyposis may be extreme

Schwarz and Oppenheim (1952) considered hypertrophic (pseudo tu

Acute gastritis

Boas (1925) subdivided acute gastritis into simple, infectious, phlegmonous and toxic forms, and Henning (1934) into exogenous, corrosive and phlegmonous types

Many acute infections are accompanied by acute gastritis (Faber, 1927) It is easily produced by a variety of agents, but most of them are systemically toxic Hot water (56°–60°C) and hydrogen peroxide (100 cc of 3 per cent solution perfused through a gastric pouch) *per se* have no systemic toxicity, but when acute gastritis is produced and maintained by these agents the animals cease eating and succumb to an intercurrent infection (Ivy, 1944)

Schindler (1947) has suggested the following histopathological classification of acute gastritis

(*a*) Acute, simple exogenous gastritis (acute gastric catarrh, acute gastrosis, food poisoning)

(*b*) Acute corrosive gastritis (toxic gastritis)

(*c*) Acute haematogenous (infectious) gastritis

(*d*) Acute phlegmonous gastritis

Chronic gastritis

Chronic gastritis assumes two distinct forms (1) atrophic and (2) hypertrophic It has been described as simple and mucous (Ewald, 1893), catarrhal, (mucous hypersecretory), hypersecretory and atrophic (Mathieu, 1898), antrum (associated with ulcer), generalized, atrophic (associated with carcinoma) (Orator, 1925), hypertrophic and atrophic (Letulle, 1931), irritative and haematogenous (Faber, 1935), hyperpeptic, hypopeptic and apeptic (Lion, 1935), exogenous and endogenous (Henning 1934, Zweig, 1935), hypersecretory and hyposecretory (Pevsner and Gordon, 1935), superficial, atrophic and hypertrophic (Schindler, 1935, Gow, 1942) and erosive, follicular and hypertrophic (Bell 1941) Schneider (1951) considered the irritable stomach as belonging to the pre ulcerative symptom complex, organic hypertrophic gastritis as tending towards ulcer formation and atrophic gastritis as tending towards carcinoma

Histopathology

Letulle (1931) differentiates the histology of hypertrophic and atrophic gastritis, the former is characterized by the thickening of the mucous membrane, the latter by the flattening and stratification of the epithelial cells

Magnus and Rodgers (1938) have pointed out that the spreading of the two types of gastritis appears to be different, atrophic gastritis tends to be patchy at first before it becomes diffuse, while hypertrophic gastritis if localized spreads uniformly and shows no patchy distribution The "état mamelonné produced by inflammation shows the additional signs of thickened and oedematous mucous membrane

According to Magnus (1946) simple gastritis may be divided into inflammatory and non inflammatory types which differ fundamentally from each

ASSOCIATION OF GASTRITIS WITH DUODENAL ULCER

According to Finsterer and Cunha (1931) in duodenal ulcer the primary seat of the affection is not in the duodenum itself but in the stomach because the antrum shows chronic inflammatory changes which produce abnormal gastric secretion

Rodgers and Magnus (1938) found in 20 specimens removed for duodenal ulcer that the body mucosa was normal in every case

Templeton and Schindler (1939) found gastroscopically that out of 75 patients with duodenal ulcer 17 had mild hypertrophic, 10 severe hyper trophic 15 mild superficial 4 severe superficial, and 3 atrophic gastritis, 11 had haemorrhagic pigment and 15 were normal Of the 130 patients with no evidence of ulcer, 42 had hypertrophic, 30 superficial 40 atrophic, and 18 both forms of gastritis

Out of 70 patients with radiological evidence of duodenal ulcer Carey and Ylvisacker (1942) observed gastroscopically 16 with normal gastric mucosa 27 with hypertrophic and 10 with superficial gastritis

Tumen and Lieberthal (1943) observed that, of 50 patients with duodenal ulcer who underwent gastroscopy 33 were found to have chronic gastritis 1 unclassified inflammatory change and 16 normal stomachs The gastritis was of the superficial type in 11, the hypertrophic type in 17, and atrophic changes were seen in 5 Freeman (1946) noted hyperplasia of the gastric mu cous membrane in 76 per cent of 50 patients with duodenal ulcer Palmer (1949) found that when duodenal ulcer was active, there was a tendency for a greater incidence of superficial gastritis which tended to disappear with the healing of the ulcer

Scheff, Horner and Kenamore (1944) observed 29 patients with pyloric obstruction due to duodenal ulcer, gastroscopic evidence of gastritis was found in 86 per cent as compared with 62 per cent of patients without obstruction

ASSOCIATION OF GASTRITIS WITH GASTRIC ULCER

Rodgers and Magnus (1938) stated that in 92 partial gastrectomy speci mens containing one or more gastric ulcers the body mucosa was affected by atrophic gastritis in 28 cases (30 4 per cent) and in the remainder it was localized in the pyloric antrum

Templeton and Schindler (1939) in comparative roentgenological and gastroscopic studies found that out of 37 patients with gastric ulcer, 22 had hypertrophic gastritis Schindler and Baxmeier (1939–40) in 317 gastroscopic examinations on 91 patients found 43 with no gastritis and 44 (44 per cent) with purpuric type lesions

Pritchett and Knies (1942) found that in 272 cases 34 per cent had hyper trophic 21 per cent chronic superficial and 11 per cent atrophic gastritis

Maher Zinninger Schiff and Shapiro (1943) who gastroscoped 14 patients with gastric ulcer found that 6 had normal, 4 superficial, 3 hypertrophic and 1 both types of gastritis Horner and Scheff (1945) found in 54 patients with

morous) gastritis a rare condition which has an unknown aetiology and pathogenesis, and appears roentgenologically and gastroscopically to be similar to malignant tumours, to be benign and to have few clinical signs and symptoms

DUODENITIS

Duodenitis or the inflammatory reaction of the first part of the duodenum assumes two forms, acute and chronic They correspond to the two fundamental types of gastritis and may be considered as identical pathological manifestations

Acute duodenitis

Acute duodenitis represents usually only part of a diffuse inflammatory reaction of the digestive mucous membranes to a generalized infection or intoxication and is a frequent manifestation in uraemia and in burns

Hunter (1890) produced acute lesions of the duodenum by injecting toluylenediamine in animals He suggested that the lesions were produced by the excretions of certain poisons through the bile

Chronic duodenitis

The relation of chronic duodenitis to the aetiology of chronic duodenal ulcer appears to parallel that of chronic (hypertrophic) gastritis to chronic gastric ulcer The symptomatology of duodenitis is identical with that of chronic duodenal ulcer

Hypertrophy of the mucosa was observed by Apperly (1923), Orator (1925), Nagel (1926), Wellbrock (1930), Rivers (1931), Kirklin (1934), Barclay (1936), and Taylor (1941)

The continuity of the stomach and duodenum explains the frequent association of chronic gastritis with chronic duodenitis (Bouchut and Ravault 1927, Konjetzny, 1928, Ramond and Jacquelin, 1935, Allessandrini, 1935, Gubergritz and Tchayka, 1936, Templeton, 1944, Debray and Pergola 1951)

According to Faber (1935) the pyloric sphincter does not act as a barrier, and in gastritis of the antrum the disease in every case passes beyond the *pyloric sphincter to involve the duodenum*

The symptomatology of duodenitis is similar to that of duodenal ulcer (Rivers, 1931, Kirklin, 1933, 1934, Barclay 1936)

The differentiation between duodenitis and ulcer is probably largely academic (Palmer, 1951) Duodenitis in association with chronic appendicitis and chronic colitis has been reported by Basset (1925), Ducuing and Fabre (1936), Brodin (1939), Brodin and Tedesco (1934, 1936 1941) These authors have observed that duodenal spasm and duodenal stasis are cured by the ablation of a chronically inflamed appendix Chiray and Amy (1930) drew attention to duodenal congestion and haemorrhages produced by chronic infections of the ileo caecal angle and by stasis in the left colon

still have hyperchlorhydria after the duodenal ulcer has been present for 10 or 20 years or more (Hurst 1935, Bergmann 1936)

Permanent anacidity in hypertrophic gastritis has never been proved (Schindler, 1947)

According to Allessandrini (1950) repeated increased gastric acid values represent a premonitory sign and may precede by several years the appearance of the ulcer

RADIOLOGICAL DIAGNOSIS OF CHRONIC GASTRITIS

According to Feldman (1945) the association of hypertrophic gastritis in cases of chronic gastric ulcer is frequently observed Roentgenologically, the mucosal folds are usually enlarged swollen and rigid in the latter In small mucosal erosions and in the early stages of gastric ulceration, swelling of the mucosal folds may not be demonstrable

The x ray appearance of chronic duodenitis has been described by Kirklin (1929) The roentgen diagnosis of gastritis is subject to considerable errors of interpretation (Buckstein 1930)

Schneider (1951) described the different aspects of gastritis as seen in the roentgenological picture in the stomach with normal form and function the mucosa shows a soft relief and regular pattern of delicate serpiginous longitudinal folds in the stomach with functional gastritis (gastrismus Reiz magen) the mucosa shows longitudinal folds with soft oblique folds and temporary mildly hypertrophied folds—this stage corresponds to the pre ulcerative symptom complex In the organic hypertrophic type the mucosal folds are enlarged in all directions and display a corkscrew pattern with cross-folds, the stomach is hypertonic and spastic and corresponds to the ulcer stage, in the atrophic type there is little mucosal relief, the stomach is hypo tonic or atonic and corresponds to the carcinomatous stage

CLASSIFICATION OF CHRONIC GASTRITIS

Chronic gastritis may be divided into two distinct categories (*a*) hypertrophic, and (*b*) atrophic

Hypertrophic Gastritis

The sequential relationship of chronic superficial (hypertrophic) gastritis and duodenitis to chronic peptic ulcer

Cruveilhier (1829–35) was the first to differentiate clearly between ulcer of the stomach carcinoma of the stomach and gastritis and he suggested that gastritis was the primary cause preceding peptic ulceration He considered them as the same disease and related the causes of chronic ulcer to the causes of chronic gastritis There was first the erosion of the mucosa by virtue of what Hunter called the ulcerative inflammation and subsequently, the erosion or ulceration became a chronic ulcer but he was puzzled why one particular spot became an ulcer whilst the remainder of the mucosa remained intact Broussais (1823) Abercrombie (1824), Kozczynski and Jaworski (1886) and

gastric ulcer, that 40 had gastritis, 26 superficial, 6 hypertrophic, 7 atrophic and 1 combined atrophic and superficial

In an analysis of 1,000 gastroscopic examinations in dyspeptic cases in the Services, Gill (1943) found that 196 had superficial, 166 hypertrophic and 34 atrophic gastritis Cutler and Walther (1945) found, gastroscopically, that of 33 soldiers in a group of 33 asymptomatic volunteers, 30 were normal and 3 had atrophic gastritis, in a group of 36 patients with duodenal ulcer 52 per cent had either atrophic or superficial gastritis, or both

Flexner and Fleishman (1940) in a *series of 256 examinations found* 29 1 per cent superficial, 17 7 per cent atrophic and 13 per cent hypertrophic gastritis In 700 gastroscopies Carey (1940) found 9 per cent had superficial, 12 per cent atrophic and 22 per cent hypertrophic gastritis

The incidence of gastritis as diagnosed gastroscopically varies according to the observer (Schindler, 1947)

AGE INCIDENCE

The age incidence of gastritis, according to Henning (1934), between the age of 10–20 years is 4 per cent, 20–30 years, 40 per cent, 30–40 years, 25 per cent, 40–50 years, 19 per cent, 50–60 years, 7 per cent, 60–70 years 5 per cent Bank and Renshaw (1939) found in a series of 50 patients suffering from superficial gastritis from the age of 10–20 years, 1 case, 20–30 years, 8 cases, 30–40 years, 14 cases, 40–50 years, 11 cases, 50–60 years 9 cases, 60–70 years, 5 cases, 70–80 years, 2 cases

Carey (1938) found the age group for atrophic gastritis somewhat older than that for superficial gastritis, 40–60 years as compared with 20–40 years None was younger than 20 or older than 59 years Schindler and Murphy (1940) considered atrophic gastritis a disease of middle life Fitzgibbon and Long (1943) found no atrophic gastritis in their group of 40 young healthy adults

The age range in hypertrophic gastritis is wide from 20 to 60 years (Carey, 1938), rarely before 20 or after 70 years (Benedict, 1943)

The duration of symptoms is difficult to ascertain because early symptoms are usually mild and may be entirely absent

RELATION OF GASTRIC ACIDITY TO GASTRITIS

Hyperacid and hypoacid forms of gastritis as described by Boas have corresponding pathological processes which can *be distinguished gastroscopically* (Korbsch, 1925)

Hypertrophic gastritis is associated with hypersecretion and peptic ulcer (Lerman, Pierce and Brogan 1933, Miller 1933, Faber 1935, Hurst, 1935a, Bergmann, 1936, Tanner, 1951), while atrophic gastritis is associated with hyposecretion pernicious anaemia and gastric carcinoma (Miller 1933 Gordon 1943, Ricketts, Kirsner and Palmer 1948, Tanner, 1951)

Porges (1935) confirmed the observations of Orator (1925) that antrum gastritis was associated with hyperacidity and corpus gastritis with subacidity or anacidity

A large majority of patients with gastritis associated with duodenal ulcer

and fatigue—with no relation to exertion Schindler and Murphy (1940) described the clinical picture as one of epigastric discomfort, poor appetite weakness, fatigue, inexplicable nervousness, sore tongue, numbness and tingling of the extremities and they considered it to be a serious disease

Similar observations were made by Jackson Swalm and Morrison (1942) Barnett (1943) considered malaise weakness, fatigue and nervousness as the *non specific tetralogy* characteristic of atrophic gastritis

Gordon (1943) distinguished two clinical entities, one with hypertrophic gastritis and symptoms resembling those of peptic ulcer and the other with general weakness numbness, sore mouth, associated with atrophic gastritis and achylia

Atrophic gastritis and pernicious anaemia

The relation of atrophic gastritis with the deficiency diseases particularly pernicious anaemia and its complications, the subacute combined degeneration of the cord is now generally recognized

Fenwick (1870) recorded the occurrence of atrophy of the gastric mucosa in a case of pernicious anaemia and made further contributions in 1877 and 1880 in which he drew attention to the regularity in the association of pernicious anaemia with atrophic gastritis Similar observations were published by many authors

Hurst (1926) showed that achlorhydria is an essential predisposing cause of Addison s anaemia, Konjetzny (1928) held a similar view

Castle, Heath and Strauss (1931) stated that the disease is due to a nutritional deficiency conditioned by a defect in the gastric secretions Atrophy of the gastric mucous membrane with a complete absence of free hydrochloric acid is the rule The gastric atrophy or atrophic gastritis is the primary disease which is responsible for the lack of the anti anaemic factor and consequent development of the pernicious anaemia

Wilkinson and Brockbank (1931) found in 291 cases of familial achlorhydria 70 (24 1 per cent) with pernicious anaemia

Magnus and Ungley (1938) found no evidence of inflammatory change but only atrophy in the mucosa in specimens taken from individuals dying from pernicious anaemia

Rivers and Smith (1940) held the view that atrophy of the gastric mucous membrane is probably a degenerative process associated with a deficiency state and that the changes in the mucous membrane are due to contractions of the muscularis mucosae

Berry and Colet (1948) considered that gastric mucosal atrophy may precede pernicious anaemia and gastric carcinoma by several years

Chronic atrophic gastritis is usually found together with a deficiency state —in pernicious and idiopathic microcytic anaemia due to iron deficiency Faber and Hurst assumed that the gastritis is the primary disease leading to the secondary deficiency state Others hold the opposite opinion and think that gastritis is due to lack of the anti anaemic factor

Bouveret (1893) held similar views as to the sequence of the inflammatory manifestation preceding the establishment of the ulcer

The view that ulcer develops on an already inflamed mucous membrane was held by Boas (1894), Mathieu (1898), Koennecke (1922), Konjetzny (1923a, b, 1930), Schmincke (1923), Aschoff (1924), Delore, Martin and Mallet Guy (1925), Bohmansson (1926), and Bouchut and Ravault (1927)

Symptomatology

The identity between symptoms of chronic hypertrophic gastritis and those of chronic peptic ulcer has been emphasised by Faber (1927), Redwitz and Fuss (1928), Buchner, Siebert and Molloy (1928), Stewart (1929), McCann (1929), Gutzeit (1929), Konjetzny (1930), Puchert (1931), Lindau and Wulff (1931), Norpoth (1932), Aschner and Grossman (1933), Roholm (1933–34), Henning (1934), Faber (1935), Pevsner and Gordon (1935), Carey (1937), Magnus and Rodgers (1938), Rivers and Smith (1940), Eusterman (1943), Benedict (1943), Wolf and Wolff (1943a), Wiley (1944), Cutler and Walther (1945), Feldman (1945), Magnus (1946), Albot and Debray (1946), Betz (1947b), Schindler (1947), Flood (1950), Bernard (1950)

The gastritis anamnesis ('Ulcuskrankheit ohne ulcus', Morawitz) is differentiated from ulcer anamnesis only by the difference in the duration of the symptoms (Schindler, Ortmeyer and Renshaw, 1937)

Atrophic Gastritis

Handfield Jones (1855) gave the first pathological description of atrophy of the gastric mucosa

According to Lubarsch (1923) "gastritis atrophicans progressiva' is a prolonged process with regenerative (or reparatory) and hyperplastic manifestations which concerns all the layers of the mucosa According to Taylor (1941) the atrophic mucosa must be considered an acquired pathological condition and hyperplastic and hypoplastic states of the mucous membrane appear to be physiological variants from the standard and are not essentially associated with disturbances of function but they are however, particularly susceptible to disease Benedict (1946–47) considered that gastric atrophy is a definite disease of the stomach It may in part be the result of an inflammatory process or in part the result of a deficiency factor As a localized process it may occur with other diseases such as ulcer or cancer As a diffused process, it may be idiopathic or associated with deficiency diseases notably pernicious anaemia

Symptomatology

Faber (1935) pointed out that atrophic gastritis more often produced general and nervous symptoms Moutier (1935b) stated that the symptoms of atrophic gastritis are more those of a general disease of the whole organism than those of a localized disease of the stomach In his series the general manifestations of the disease were much more striking than the digestive symptoms The single outstanding complaint was a feeling of intense weakness

a gruel meal and in 56 per cent it was excessive Molofsky and Hollander (1951) found that most of the reports describe this component of the gastric secretion as sparse and mucoid

Secretory depressant in pernicious anaemia

Brunschwig Van Prohaska, Clarke and Kandel (1939) observed that the gastric juice of patients suffering from pernicious anaemia when injected intravenously into dogs with gastric pouches, produced anacidity and a pronounced although transitory, depression of the volume of secretion but Brunschwig Rasmussen, Camp and Moe (1942) demonstrated that the *depressant factor is also present in the gastric secretion from dogs pouches* acid human gastric juice, and achlorhydric gastric juice from patients without pernicious anaemia or carcinoma of the stomach

Effect of substitution treatment

Brown (1934) observed no noticeable change after substitution treatment Benedict (1935) found that following specific therapy of pernicious anaemia, evidence of atrophy and hypertrophy of the stomach have both tended to disappear Regeneration of the mucosa by liver therapy is believed by Magnus and Ungley (1938) to be unlikely from the very nature of the lesion Olson and Heck (1945) recorded that the mucosa increased in thickness from 0 6 mm before treatment to 0 85 mm after treatment but never returned to the normal 0 98 mm

Palmer (1949) described a case of diffuse chronic atrophic gastritis which recovered completely after substitution therapy

According to Molofsky and Hollander (1951) achlorhydria in pernicious anaemia appears to be a permanent feature and is unaltered by treatment

Atrophic gastritis and gastric carcinoma

The relation of gastritis to gastric carcinoma has been pointed out by many authors particularly since Broussais and Cruveilhier have drawn attention to it Rosenheim who in 1888, studied the relation of the atrophic processes of the gastric mucous membrane to carcinoma described a case in which atrophic paths were found at some distance from the tumours

Konjetzny (1913 1934) believed that carcinoma never develops on a healthy mucous membrane and that although the factors concerned with carcinogenesis are not known, the carcinomatous lesion must nevertheless be considered as the end stage of a short or long series of morbid processes which is invariably accompanied by a well defined chronic atrophic hyperplastic gastritis

It is generally held that atrophic gastritis precedes carcinoma (Hurst 1932 Usland 1935, Moutier 1936 Kapp 1937 Comfort Butsch and Eusterman 1937, Shapiro Schiff Maher and Zinninger, 1942, Guiss and Stewart 1943) Schindler (1941) admits that atrophic gastritis is a precursor of gastric cancer and therefore, these patients should be watched carefully Jankelson McClure and Freedberg (1943) found that 2 out of 18 cases of

The secretion of hydrochloric acid in pernicious anaemia

Free gastric acid was absent or almost absent in the cases recorded by Faber and Bloch (1900), Stockton (1904), Cabot (1908), Austin (1911), Friedenwald and Morrison (1919), Percy (1920), Ewald (1920), Zadek (1921), Levine and Ladd (1921), Hurst and Bell (1922), Panton, Maitland Jones and Riddoch (1923), Faber and Gram (1924), MacBride and Carmichael (1925), Grinker (1926), Evans (1926), Morawitz (1930), Strandell (1931), Sturgis and Isaacs (1931), and Kahn (1932) Similar results were found in response to the injection of histamine by Davies (1931), Wilkinson (1932), Haden (1932), Helmer, Fouts and Zerfas (1932), Hartfall (1933) Bloomfield and Polland (1933), Sturgis (1936), Goldhamer (1937), Rozendaal and Washburn (1938), Ihre (1938), Morrison (1938)

Chlorides in pernicious anaemia

Total chloride concentration in gastric juice has been usually found to be low in pernicious anaemia (Miller and Smith, 1927b, Wilkinson, 1931, Helmer, Fouts and Zerfas, 1932, Hartfall, 1933, Ihre, 1938)

Secretion of pepsin in pernicious anaemia

There is a concensus of opinion that secretion of pepsin is considerably reduced, if not completely abolished, in patients with pernicious anaemia (Fenwick, 1870, 1880, Stockton, 1904, Levine and Ladd, 1921, Faber and Gram, 1924, Faber and Holst, 1928, Johansen, 1929, Polland and Bloomfield, 1930, Davies, 1931, Wilkinson 1931 1932, Helmer, Fouts and Zerfas 1932, 1934, Hartfall 1933, Maltby, 1934 Vanzant, Osterberg Alvarez and Rivers, 1936, Toby, 1937, Ihre, 1938 Witebsky Klendshoj and Vaughan 1942)

The administration of histamine in pernicious anaemia patients provokes negligible pepsin values of little significance Vagal stimulation by insulin hypoglycaemia, which has been shown to be a very potent stimulus for peptic secretion, does not appear to produce any peptic secretion in these patients Wilkinson and Brockbank (1931) observed that 50 per cent of the cases of pernicious anaemia which had achlorhydria also had no peptic activity, that is achylia gastrica Greenspan (1936) believed that pepsin is normally capable of inactivating the anti pernicious anaemia intrinsic factor, and that since the enzyme is bound by dietary protein its inactivation of the anaemic factor is thus prevented, but these observations have not been confirmed by other investigators (Helmer Fouts and Zerfas, 1934, Castle and Ham, 1936, Fitz Hugh and Creskoff 1936, Morrison 1940, Bockus 1943)

Mucus in pernicious anaemia

Wilkinson (1932) noted considerable mucus in the specimens from his 208 cases obtained by fractional analysis After administration of histamine this was reduced to negligible quantities and after acetylcholine there was also a definite decrease Hartfall (1933) found mucus present in all cases after

gastritis or a combination of the two, whilst mucosal haemorrhage occurred in 22 per cent Gray (1943a) found in 100 alcoholics with epigastric symptoms 22 with superficial gastritis 3 with atrophic, 8 with combined superficial and atrophic 1 with localized hypertrophic and 1 with hyperplastic nodular gastritis

Post operative Gastritis

Gastritis is the most frequent complication of the post operative stomach It is invariably of the hypertrophic type The mucous membrane is generally found to be swollen and oedematous erosions and hypertrophic nodes may be present It may involve a portion or the entire gastric remnant

Korbsch (1933) observed gastroscopically inflammatory changes of the stomach after every gastric resection According to Korbsch (1941) it is more frequent after Billroth II than after Billroth I and is invariably present after gastro-enterostomy

According to Schindler, Necheles and Gold (1939), if free acid is present the canine stomach may develop various gastritic manifestations during surgical procedures

A large proportion of cases of gastritis following gastro-enterostomy and gastrectomy was observed gastroscopically by Moutier and Ghelew (1939), Flexner and Fleischman (1940), Taylor (1941) Pritchet and Knies, (1942), Brown and McHardy (1944), Tosseland and McDonald (1945) Vitkin (1945), Boller (1947) Schindler (1947), Gray Myers and Dockerty (1948), Palmer (1948), and Drown (1950)

According to Paulson and Gladsden (1949) vagotomy does not protect against post-operative gastritis Pritchett and Knies (1942) believed that the introduction of enteric enzymes into the stomach was to blame Boller (1947) considered trypsin as the primary element responsible for the initial trauma Steinberg (1951) suggested that bilious regurgitation which causes gastritis is one of the post gastrectomy disabilities

The behaviour of the anastomotic stoma is referred to in the Chapter which deals with the Pyloric Sphincter page 91

Conclusions

Generally speaking one may distinguish two types of gastritis (1) the gastritis which is associated with peptic ulcer, and (2) the gastritis which is associated with carcinoma and the deficiency diseases They are histologically different the former being of the hypertrophic and the latter of the atrophic type

Ulcer gastritis shows a mucous membrane with a well conserved parenchyma with the usual signs of an inflammatory reaction an exudate with leucocytic infiltration and migration of polymorphonuclear leucocytes through the epithelium of the glands, pits and villi and the appearance of erosions It is not progressive and shows little further involvement after the initial reaction has taken place

Cancer gastritis shows a mucous membrane with a generalized disappear

primary atrophic gastritis, followed up for 2 years, had developed a polyp Barrett (1946–47) thinks it reasonable to assume that if all cases of gastritis were followed from inception, 80–85 per cent of these patients would be found to be suffering from gastric cancer

Pernicious anaemia and carcinoma

Most observers maintain that pernicious anaemia and carcinoma coexist accidentally Some believe that pernicious anaemia develops as a result of carcinoma of the stomach, others are of opinion that only the blood picture of pernicious anaemia occurs but that true pernicious anaemia does not result from carcinoma of the stomach

Pernicious anaemia preceding gastric carcinoma has been reported by Brandes (1921), Conner and Birkeland (1933), Silverman (1936), Rambach (1936), Washburn and Rozendaal (1938), Jenner (1939), Rhoads (1940–41), Rigler (1943), Schindler (1947), Hardt, Schwartz and Steigmann (1948), Bourne (1948), and Mosbech and Widebaek (1950)

The common basis of atrophy of the gastric mucous membrane in carcinoma of the stomach and the deficiency diseases points to the fact that this may constitute a common aetiological factor and, as predicted by Hurst (1935) who observed 5 cases of carcinoma of the stomach associated with pernicious anaemia and subacute combined degeneration of the cord, that the prolongation of life of patients suffering from pernicious anaemia would lead to a development of carcinoma in these patients, since he considered the chronic gastritis as a pre cancerous condition

Palmer (1944) showed the illustration of a case of intraluminal gastric carcinoma of a patient, a male aged 58 years who developed pernicious anaemia in April 1926 He responded well to the oral administration of whole liver, but developed a pedunculated gastric polyp (adenocarcinoma) which was removed in November 1926 In 1934 a large tumour (alveolar colloid carcinoma) was found on the greater curvature and removed by subtotal gastrectomy The patient was in good health 9 years later when he reached the age of 75 years

Kaplan and Rigler (1945) believed that there is some evidence, although not conclusive, to indicate that hereditary factors conditioning the development of pernicious anaemia and gastric carcinoma may be linked in some manner to explain the co existent occurrence of the two diseases in the same individual, and they quote Conner (1929) who effectively demonstrated the hereditary basis of achlorhydria in patients with pernicious anaemia

According to Kaplan and Rigler (1947) a statistical analysis reveals that pernicious anaemia and carcinoma of the stomach develop in the same individuals more often than would be expected on the basis of chance alone and that they must, therefore, be aetiologically related

Alcohol gastritis

Gray and Schindler (1941) found in 100 cases of chronic alcoholics that 55 per cent had a normal mucosa and 45 per cent had mainly superficial

gastritis or a combination of the two, whilst mucosal haemorrhage occurred in 22 per cent Gray (1943a) found in 100 alcoholics with epigastric symptoms 22 with superficial gastritis 3 with atrophic, 8 with combined superficial and atrophic 1 with localized hypertrophic and 1 with hyperplastic nodular gastritis

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Cancer gastritis shows a mucous membrane with a generalized disappear-

ance of the parenchyma with excessive proliferation of the connective tissue and with predominating lymphocytes and plasma cell infiltration It starts as a patchy condition, appears to spread progressively until it has invaded the whole organ and is irreversible

The fact that hypertrophic gastritis is associated with hyperchlorhydria and atrophic gastritis with achlorhydria explains the presence of hydrochloric acid in the stomach in association with atrophic gastritis, at a stage before the latter condition completely abolishes the secretory function of the stomach

Stempien, Oritt and Karr (1953), who correlate hypertrophic gastritis with hyperfunction and superficial and atrophic gastritis with hypofunction, consider that mixed gastritis correlates with a summation of zones of hyper function and zones of hypofunction, the level of acid secretion is a resultant of the physiological rate of secretion plus or minus the type and degree of mucosal pathological change

AUTHOR S CLASSIFICATION OF CHRONIC GASTRITIS

The characteristic features of the two main types of chronic gastritis are so strikingly different and their causation and evolution so obviously divergent that the marked contrast of their causation and of their symptomatology may be used as the basis for a simple clinical classification (Spira 1944)

Chronic gastritis may be classified according to whether it is produced (*a*) by direct, or (*b*) by indirect causes

Direct causes

Direct causes are acquired they produce *local* manifestations and reactions which are reversible They are associated with inflammatory processes increased acid secretion and gastric hypertonus, this stage corresponds to the syndrome of hyperfunction which may lead to chronic peptic ulcer formation There is an increase of appetite and a tendency to constipation relief of symptoms and cure of the lesion is achieved by the removal of the offending agent They are caused by

(*a*) *Chronic superficial* or *catarrhal* gastritis produced by mild repeated irritation

(*i*) Mechanical thermal chemical factors (alcohol tobacco drugs highly spiced foods)

(*ii*) Swallowing of purulent material (chronic infections of post nasal gingival pulmonary, intestinal origin)

(*b*) *Chronic hypertrophic* gastritis produced by severe repeated irritation

(*i*) Marked effect produced by persistent regurgitation of bile into the stomach (failure of the pyloric sphincter post-operative)

(*ii*) Persistence of chronic superficial gastritis

Indirect causes

Indirect causes are mostly inherited they produce *systemic* manifestations with local reactions which may be irreversible They are degenerative processes associated with decreased acidity and gastric hypotonus which may lead to gastric carcinoma There is a decrease in appetite and a tendency to diarrhoea they are beneficially influenced by the appropriate substitution treatment They are caused by

(*a*) *Primary factors* associated with deficiency diseases Simple microcytic anaemia Addisonian anaemia Subacute combined degeneration of the cord They are produced by a process of glandular *transformation*

(*b*) *Secondary* factors associated with other pathological conditions

(*i*) As a sequel to virulent acute gastritis They are produced by a process of glandular *destruction*

(*ii*) In pyloric stenosis After intesive alkaline treatment Achlorhydria of old age They are produced by a process of glandular *exhaustion*

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PART IV

THE PATHOGENESIS OF CHRONIC PEPTIC ULCER

The theories of ulcer formation will be critically reviewed before giving the elements which lead to the postulation of the author's theory

CHAPTER 11

THE THEORIES OF CHRONIC ULCER FORMATION

Many attempts have been made to produce a chronic peptic ulcer by artificial means Although innumerable methods resulted in a structural defect of the wall of the alimentary tract, the experimental lesion invariably proved to be an acute one and no method has as yet succeeded in producing in the ulcer bearing area of an animal the chronic lesion which occurs spontaneously in man

THE VASCULAR THEORY

Virchow (1853) thought that peptic ulcer was due to a local embolus or thrombus which interfered with the circulation and lead to infarction of the gastric area supplied by the affected vessels but Cohnheim (1890) pointed out that most patients have not reached the age in which vascular changes are found Katzenstein (1908) suggested that the following formula may explain ulcer formation CN + A + V = ulcer C = defects of circulation (Virchow) N = eventual necrosis, A = (hyper) acidity V = digestive power of pepsin Stasis or spasm of the capillary vessels was suggested by Muller and Heimberger (1924), Duschl (1924), Berlet (1924) Nothaas (1938) Boles, Riggs and Griffiths (1939) Brun (1942) Wener Hoff and Simon (1948) De Busscher (1947) found that the vascularization uniformly increases in relation to the concomitant gastritis of chronic ulcer, all the vessels of all the layers of the stomach contribute to the dense vascular net which surrounds the ulcer His study refutes the aetiological vascular factor in the pathogenesis of ulcer

It should be noted that ligation of blood vessels does not produce ulcers (Litthauer, 1909, Ivy 1920, Layne and Bergh 1943 Lannin 1945, Betz, 1947a Leveen 1948, Baronofsky, 1948 Holm Boyarsky and Morrione 1949)

Arteriovenous shunts

De Busscher (1948) believed that the dysfunction of the arteriovenous ana stomoses (opening and closing) leads to alteration of the tissues exposing the mucous membrane *to many noxious factors which reduce its resistance and* that the ulcer patient is constitutionally predisposed to dysfunction of the arteriovenous anastomoses which play a part in the genesis localization healing and evolution of the ulcer

Barclay and Bentley (1949) made arteriographs of the gastric wall on

1923, Löhr, 1924, Bitter and Lohr, 1926, Duval and Roux, 1926, Ricen, Sears and Downing, 1928, Henning, 1930, Teale, 1934, Barber and Franklin, 1946)

Rosenow (1913) pointed out that haemorrhage, superficial erosions and definite ulceration of the mucous membrane of the stomach and duodenum occur during severe infections in man and in experimentally infected or otherwise severely intoxicated animals He showed that the intravenous injection of streptococci of the proper grade of virulence may be followed by ulcer of the stomach and duodenum but in a paper entitled *Elective localization of streptococci* Rosenow (1915) in 833 experiments with 220 strains of streptococci observed lesions distributed as follows joint lesions, 27 per cent, stomach and duodenum (with haemorrhage and ulcer) 28 per cent, appendix, 5 per cent, gall bladder, 11 per cent, pancreas 6 per cent, intestines, 8 per cent, myocardium, 10 per cent, muscles, 12 per cent, kidney, 9 per cent, lung 11 per cent, skin 2 per cent, eye, 3 per cent The variety of these lesions clearly demonstrates the lack of specificity of the microbe for the stomach

Gerdine and Helmholtz (1915) found in 10 out of 14 ulcers, diplococci and streptococci in the ulcer base which they believed to be of aetiological significance and, therefore supported Rosenow's (1915) views At necropsy these authors isolated a *Streptococcus viridans* from the ulcer which, when injected into dogs and rabbits produced haemorrhages and ulceration in the pyloric end of the stomach and in the duodenum Reference, however, to the protocols shows that the primary disease from which the very young infants died were perforated duodenal ulcer, 1 case, tuberculous meningitis 1 case miliary tuberculosis, 2 cases, atrophy, multiple ulcers of the duodenum, 3 cases, and 1 case each of purulent meningitis acute splenic tumour, bronchopneumonia and gastro-enteritis Gerdine and Helmholtz also emphasized the appearance of duodenal ulcer in epidemic form. Ivy (1920) did not find it possible to produce ulcer by direct infection of the gastric mucosa in dogs with organisms isolated from gastric ulcer in man by Rosenow's technique

Nickel and Hufford (1928) found septic foci in almost every case of peptic ulcer The causative streptococcus was isolated from the resected ulcer as well as from the foci of infection and produced electively, similar lesions of the stomach and duodenum when injected intravenously into rabbits In support of their view the authors produced illustrations which show diffuse submucous haemorrhages thus clearly demonstrating the acute variety of the lesion which does not become chronic

Pulvertaft (1929) considered it unnecessary to postulate an elective localization of the streptococcus (Rosenow 1915) since such lesions could be produced by streptococcal toxins entirely free of organisms

Alvarez (1932a) pointed out that while an ulcer should heal better when not bathed day and night by infectious material, the fact that ulcers are seen most commonly in cases which have the most bactericidal gastric juice strongly militates against the infectious cause of ulcer

Attempts which have been made to induce chronicity in artificial acute

stomachs removed from the cadaver or excised at operation for duodenal ulcer They observed arteriovenous anastomoses in the region of the submucous plexus of vessels, the opening of which excludes active circulation through the vessels of the mucous membrane When the peritoneal cavity is opened and the stomach handled at operation, the shunt comes into play and this condition persists in the excised stomach wall after the operation When the sympathetic outflow to the stomach is blocked by means of a spinal anaesthetic the shunts do not open If resection is performed under general anaesthesia, leaving the sympathetic pathways open to convey the efferent impulses from the abdominal wall, the injection material does not enter the mucosa Walder (1950) by the introduction of glass spheres of known diameter (60–180 μ) into the perfusate entering the arterial side of the circulation of human stomachs removed at operation examined for their presence in the venous outflow, demonstrated that arteriovenous shunts are many times greater in diameter than the capillary vessels Doran (1951) did not confirm the observations of Barclay and Bentley (1949)

The principle that blood may be diverted from the superficial parts of an organ to pass through its deeper regions as described by Trueta, Barclay, Daniel, Franklin and Prichard (1947) for the kidney, was shown to apply also to the liver (Daniel and Prichard, 1951), and the liver, spleen and lungs (Prinzmetal, Ornitz, Simkin and Bergman, 1948), and to the lungs of man with little or no pathology (Tobin and Zariquiey, 1950, Brink, 1950) These are considered to be transmitted phenomena during the course of vascular recovery from total constriction produced by sympathetic activity (Del Pozo, Hernandez Peon, and Guzman, 1952)

Clara (1939) suggested a universal occurrence of arteriovenous anastomosis as occurring in all organs and tissues of the body *

THE INFECTIVE THEORY

A great deal of attention has been given to direct infection of the mucous membrane as the primary cause of peptic ulcer

It is of interest to remember that the meconium of the new born infant is sterile that bacteria in the stools appear only after the first feed has been given and that food is the most important source which introduces the organisms found in the stomach It is generally admitted that in healthy persons gastric juice is capable of destroying most of the organisms which enter the stomach (Spallanzani, 1784, Korte, 1875, Bunge, 1890, Hewetson, 1904, Bolton 1910, 1913, Hayem 1911, Dawson, 1911, Rosenow, 1921, Knott,

* *Vessels of the ulcer bearing area* Reeves (1920), Jatrou (1920), Hofmann and Nather (1921) and Berlet (1923) have suggested that the blood vessels of the lesser curvature and of the first part of the duodenum are fewer of a different type and with fewer anastomoses than those of the rest of the stomach Bauer (1923) has suggested that they are the expression of an incomplete adaptation of the Magenstrasse (which represents a rudimentary organ like the appendix and which is seen especially in ruminants but also according to Keith and Jones in primates (semnopithecus) He observed that experimental lesions healed slower in the Magenstrasse than in other parts of the stomach

cotonia of Eppinger and Hess have unquestionably been disappointing The maintenance of the autonomic balance or dynamic equilibrium is achieved by many elements Warter and Fitzenkam (1949) admit a double symptomatology in the ulcerative disease (1) the digestive syndrome, and (2) the nervous syndrome, but, because neurological symptoms persist after gastrectomy, they reject the view that the neurological signs may be secondary to the ulcerative lesion Fulton (1949 a) stated that the concept of sympathicotonic or vagotonic individuals, though it contained an element of truth, is now discarded for the same individual exhibits sympathetic and parasympathetic manifestations in different situations and both are frequently called into play at the same time in a selective manner Little (1953), in 50 male patients with peptic ulcer selected at random and of an average age of 43 years, could not find a significantly greater number of parasympathetic signs than were found in patients without ulcer

Organic lesions

Cushing (1932) drew attention to the association of peptic ulcer with cerebral tumours Winkelstein (1945) reported that the majority of cases of duodenal ulcer in boys aged 11–17 years was associated with signs of pituitary deficiency correlated with periods of special emotional stress Of 342 patients in the German Air Force, who received traumatic brain lesions during World War II Kalk (1945) could not find a single case of chronic peptic ulcer

Laruelle and Reumont (1949) concluded that injury to the parasympathetic and orthosympathetic centres the vagal and splanchnic ganglions the solar and mesenteric plexuses produce identical lesions making their interpretation difficult particularly in view of the clinical improvement following vagotomy for chronic ulcer There is little experimental evidence to support the view that irritation of the nervous elements of the gut is involved in ulcer production (Best and Orator, 1932)

The psychosomatic theory

Bauer (1934) emphasized that the psychic side of an individual is involved in all kinds of somatic disorders and vice versa, and that primary psychic changes may have far reaching repercussions upon physical function of all kinds

McDowall (1934) recalls that in dyspepsia resulting from emotional states such as worry and anxiety or in excessive mental work we have a relic of the fact that animals under emotional stress do not partake of food the alimentary canal being brought to a standstill by contraction of all the sphincters and relaxation of the bowel wall

Robinson (1936) stated that ulcer is found only among the susceptible individuals of white races usually the long thin type who are given to worry and nervous irritability The fact that ulcer is preceded by gastroduodenal hypermotility and hypersecretion—a condition constantly found in emotional states—is significant according to McGregor (1938) and

defects of the gastric mucosa by infecting such lesions with *B coli*, staphylococcus, streptococcus and other bacteria failed completely (Ivy, Grossman and Bachrach, 1950)

THE NERVOUS ELEMENT

In considering the nervous element in the pathogenesis of peptic ulcer some differentiation must be made between the neurogenic and the psychosomatic approach to the problem, the former being concerned more with organic and the latter with the psychological disturbances of the nervous system although a sharp distinction between the organic and the functional is often untenable (Newman, 1941)

The neurogenic theory

The neurogenic theory may be studied from two aspects (1) the para sympathetic hypertonus, and (2) the organic lesions

Parasympathetic hypertonus

Much importance has been given to the observations that gastric and duodenal ulcers are commonly associated with parasympathetic hypertonus Eppinger and Hess (1909) attempted to explain the formation of the ulcers and the concomitant secretory and muscular disturbances to some disharmony in the relation of the vegetative nervous systems anaemia of the muscularis is caused by spasm through reflex action and a local ischaemia through obliteration of the arterioles, necrosis and erosions are produced, aggravated by hyperchlorhydria which is usually present in vagotonic subjects

Bergmann (1913, 1926, 1936) expressed the opinion that the entire complex of nervous symptoms associated with gastric and duodenal ulcer is referable to autonomic dysfunction which manifests itself in vasomotor disturbances The conception of Eppinger and Hess has found support from several authors, mainly in Germany (Westphal, 1914, Durante 1916, Katsch, 1924, Kalk, 1924, Mucci 1926, Muller, 1926 Wolff and Thomas, 1927, Russ, 1931, Draper and Touraine 1932 Stohr, 1934, Westphal and Kuckuck 1934, Steinberg and Starr, 1934 Barron and Curtis 1937b, Davies and Wilson, 1937, Balo, 1941, Berg, 1942, Held and Goldbloom 1946 Ruesch, 1948, Hetenyi, 1950, and Babkin, 1950)

Carlson, Boyd and Pearcy (1922) called for new definitions of the terms "vagotonia and 'sympatheticotonia' as used in clinical medicine because the stomach (including the cardiac and pyloric sphincters and the lower oesophagus) and the small intestine are under motor and inhibitory control both of the vagi and the splanchnic efferents which render untenable the view of physiological antagonism of the vagi and sympathetic for this part of the viscera Loeper and Marchal (1926) rejected Bergmann's view because they believed that ulcer is the cause of the vagal neuritis which is secondary to an ascending neuritis

Darrow (1943) pointed out that the actual clinical and physiological consequences of the concept of balance, sympathicotonia and parasympathi

constituted a large part of the disability due to medical causes in the Army of the United States of America during World War II, were found to be best treated not by sedatives diets, antispasmodics, rest or hospitalization, but by dealing with personality disturbances directly and promptly In patients with symptoms superficially resembling ulcer, 80 out of 100 studied were found to have psychoneurotic symptoms which rendered them unfit for military duty Among the actual ulcer patients, only 6 per cent were rendered ineffective by psychoneurosis Moses (1946) studied 25 unselected cases of ulcer in the Navy during World War II and found 76 per cent in the dominant *alpha* group (4 times the expected number) The ulcer cases were characterized by marked feelings of insecurity associated with strong passive dependent trends

Gainsborough and Slater (1946) found that the incidence of extraordinary causes of psychological stress was small in fact the stresses were those of ordinary life They found the results of treatment disappointingly poor, none of the psychiatric findings, not even the various indications of anxiety tendencies had any prognostic meaning

While the hypothesis of the implication of the nervous system in pathogenesis of ulcer may not readily explain the occurrence of ulcer in infants and young children or the large group of ulcer cases seen in adolescence, it was according to Brown (1946) quite consistent with clinical experience with peptic ulcer as it occurs in adult patients Kapp, Rosenbaum and Romano (1946–47) confirmed Alexander s hypothesis that the fundamental psychological factor in this disease is a conflict over intense dependent desire Winklestein (1947) believed that peptic ulcer is probably a psychosomatic disease Radloff (1947) made observations on 543 cases of peptic ulcer in 3,695 admissions to the Army General Hospital in Hawaii, 95 6 per cent of the total were duodenal ulcers He found that the psychoneurotic subjects seldom developed peptic ulcer and rarely gave a history suggestive of ulcer Palmer, Kirsner Ricketts, Maimon and Dashiell (1947) were not convinced that patients with peptic ulcer differ essentially from the ' normal , or that the role of emotional components in the formation of peptic ulcer or its recurrence has as yet been accurately assayed Douglas (1947) found that contrary to what might be expected living conditions in London during World War II appear to have had little effect on the end results of treatment of peptic ulcer Kirsner, Palmer Ricketts Dashiell and Buser (1948) admit that the role of emotional factors in the production of peptic ulcer and in its recurrence is still an enigma

Flood (1948) who followed a group of 233 patients for an average period of 6 9 years noted that emotional trauma and feelings of insecurity were the commonest precipitating factors preceding recurrences but aetiological significance was not attributed to such factors because they were frequently absent in patients with symptoms of ulcer or present in individuals who remained asymptomatic According to Gauss (1948) under the psychosomatic concept of peptic ulcer the exciting factor of the disease is the stress and strain of life the unfavourable reactions of the environment, economic malad

therefore, psychic features must be considered in the pathogenesis of peptic ulcer, although the psychogenesis is unspecific or indirect

Steigman (*1936*) observed a psychogenic factor in the Negro—finding a 12 7 per cent incidence—but it is noteworthy that he found a vast difference between the northern and southern Negro Wilson (1939) and Draper and Touraine (1942) contended that the ulcer patient is a neurotic patient In a subject with a permanent gastric fistula through which the gastric mucosa could be observed directly, Wolf and Wolff (1942b) observed pallor of the mucous membrane and inhibition of gastric secretory activity and motility during emotions such as fear and sadness, which involved a feeling of withdrawal During emotional conflicts involving anxiety, hostility and resentment they observed increased gastric secretory activity, hypermotility and hyperaemia and engorgement of the gastric mucosa Crider and Walker (1948a), who made direct observations of the interior of the stomach through a large gastrostomy opening in a Negress, aged 21 years, observed that anger, resentment, fear and anxiety were associated with decreased motility and output of acid and blanching of the mucosa Mechanical stimulation in the region of the cardiac sphincter induced heartburn, nausea, retching, and a reflux of bile stained fluid Hypersecretion and hypermotility were absent under conditions of sustained emotional tension

Mittelman and Wolff (1942) observed an association of physiological function and affective reactions which were always accompanied by an increase in hydrochloric acid, mucus and pepsin secretions Peristaltic activity became continuous and contractions increased in magnitude Rubin, Bowman and Moses (1942) found that 70 per cent of the ulcer cases had a dominant *alpha* index as opposed to the 20 per cent incidence in normal individuals

Halliday (1943) suggested a concept of psychosomatic affections which he defines as "a bodily disorder whose nature can be appreciated only when emotional disturbances (psychological happenings) are investigated in addition to physical disturbances (somatic happenings) The affections are numerous and comprise many of the common diseases of general medicine In the gastro intestinal system he considered duodenal ulcer, mucous colitis, visceroptosis, ' stress dyspepsia , some cases of constipation as definite, and gastric ulcer, gall bladder disease, haemorrhoids (non traumatic) as possible psychosomatic affections

Kalk (1945) pointed out that if the increase of perforations reported during periods of intense bombing in England and Germany was produced by psychosomatic causes no such observations could be made with flying personnel who were constantly submitted to mental stress

Cathcart (1946) classified peptic ulcer and conditions commonly referred to as "gastric neurosis ' or "functional dyspepsia' in the same group, and claimed that a close kinship exists between peptic ulcer and psychic neurosis anxiety types which was seen statistically in hospital admissions in the Canadian Army where an amazing parallelism was found in the hospitalization incidence of peptic ulcer and anxiety neurosis On the other hand Halstead (1946) observed that functional gastro-intestinal disorders, which

Doll and Pygott (1952) found that the psychosomatic element was not influenced by giving phenobarbitone (and ascorbic acid) and that it did not increase the rate of healing of gastric ulcer as judged by measurements of the ulcer crater in the radiograph

It is of particular interest to record with regard to the pathogenesis of ulcers the observation of Beaumont (1833) that when Alexis St. Martin became very angry, much bile regurgitated into the stomach

Conclusions

The psychological element as an important role in the manifestations of disease in general is easily admitted It cannot be denied that there exists an intimate relationship between the psyche and the soma and that they function normally in harmonious partnership, but to relate all bodily manifestations to mental as opposed to physical processes is to ignore the existence of the autonomic nervous system, which acts as their intermediary in the transmission of both the afferent and efferent impulses Since the body and the mind affect each other it becomes imperative to establish the seat of the primary affection which is responsible for the disruption of the physiological equilibrium before dealing with the repercussions it produces

If it be admitted that a chronic peptic ulcer is caused by a local, that is to say, somatic injury, one can also readily concede that it has psychological repercussions which constitute the secondary manifestations of the disease process On the other hand, it can be readily agreed that psychic influences produce physical reactions which manifest themselves by somatic effects It is generally recognized that psychic stimuli increase the motor and secretory functions of the stomach and that the psychic phase of digestion is dependent on the integrity of the vagus nerve but there is no evidence to support the view that the exaggeration of this function leads to ulcer formation The suggestion of the leader writer of the *British Medical Journal*, 2 1136 1951) on the subject of Psychosomatic Medicine ' that psychosomatic is an unnecessary term and the sooner it is dropped from the current literature the better should strongly be supported

THE ULCER DIATHESIS'

(*The hereditary constitutional factor*)

Bolton (1913) stated that there is no satisfactory evidence that hereditary influences play any part in the causation of gastric ulcer Hayem and Lyon (1913) held a similar view

Heredity as an aetiological factor in peptic ulcer was supported in Germany by Spiegel (1918) Heissen (1920) Strauss (1921) and Bauer and Aschner (1922) Palier (1923) defined gastric ulcer as a constitutional disease with local manifestations but made no distinction between the acute and chronic lesion Draper Dunn and Segal (1924) suggested that patients with ulcer have certain characteristic anthropometric relations and certain psychological factors which are measurable components of the 'ulcer constitution

justment, *financial uncertainties, domestic uncertainties, social upheavals,* impending calamities, frustration of any origin, in fact any of the numerous causes that threaten to disturb the peace and equanimity of a well ordered life or threaten to impede the achievement of a desired goal [On this count the majority of the adult population must be suffering from ulcers!]

Brown, Breshnahan, Chalke, Peters, Poser and Tougas (1950) administered the Rorschach test under standard conditions to a group of 25 patients with duodenal ulcer and an equal number of cases with various non gastro-intestinal diseases From the interpretation of their tests they concluded that ulcer patients as a group tend to deal with their environment at an impulsive, emotional, immature level to conflict in the area of social interpersonal relationship According to Grossman (1950) there is no clear evidence to indicate that gastric dysfunction due to emotional stress can lead to ulceration

The failure of home life *as a psychosomatic factor in the aetiology* of duodenal ulcer has been stressed by Mittelman and Wolff (1942), Moses (1946), Kapp, Rosenbaum and Romano (1947) and Ruesch (1948), but denied by Brown (1950) and Hamilton (1950) Kellock (1951) investigated the possible aetiological importance of personality in subjects with duodenal ulcer by comparing the childhood background of a group of 250 male patients with duodenal ulcer and a similar group of patients with other diseases His findings suggested that there is no difference between people with duodenal ulcer and others in the size, composition or social class of the *family into which they were born, in their educational standard at school,* or in illness in childhood Neither do duodenal ulcer patients seem to be more fortunate or less fortunate than others in the early separation from parental influence In none of the points investigated could Kellock confirm the findings of other authors—he suggested, therefore, the possibility must be considered that the "ulcer personality" may be the effect rather than the cause of the disease

Grace, Wolf and Wolff (1950) observed in two fistulous human subjects a large segment of prolapsed colon, with the mucosal surface exposed Over *whelming situations provocative of abject fear and dejection,* were associated with hypofunction of the large intestine with pallor, relaxation and lack of contractile activity Stressful life situations provocative of conflict, anger, resentment, hostility, anxiety and apprehension were found to be associated with hyperfunction of the colon manifested by hyperaemia, hypermotility and increased secretion of the enzyme lysozyme Protracted hyperfunction resulted in increased fragility of the colonic mucosa and, at times, spontaneously occurring submucosal haemorrhages

Wolf and Glass (1950) observed in their fistulous subject that after central vagus stimulation with insulin or during sustained personal conflict with anxiety and resentment HCl, pepsin and muco-protein (the glandular product) concentrations were increased while the concentration of muco proteose (the secretion of the lining columnar epithelium) was low Under the circumstances the membrane was red and engorged and there was the greatest evidence of susceptibility of the membrane to injury

tions of Young (1933) on 1,212 children that physical constitution is not related to disease

According to Robinson (1935) peptic ulcer is shown to possess racial, anthropometric, personal sex and site selectivity

Dogra (1940a) investigated 258 cases of proved peptic ulcer at the Government General Hospital, Madras High familial incidence was shown but the evidence available was not considered sufficient to support a diathesis theory He suggested a common environmental factor, as existing under the joint family system which is an outstanding feature of life in southern India, as being the cause of a very high familial incidence The disease occurs amongst all religious groups but mostly affects the extremely poor and the non Brahmin Hindus Among the Brahmins and the well to-do it is extremely rare

Wangensteen and Lannin (1942) claimed that the patients become 're-habilitated completely by being rid of their ulcer diathesis by a satisfactory operation

Edwards and Copeman (1943) obtained a family history of ulcer in more than 50 per cent of 139 cases in an army hospital Gainsborough and Slater (1946) in a group of 130 men and 32 women, found an incidence of 9 5 per cent of gastric disease in the fathers of their patients, which suggested the existence of a hereditary constitutional factor, but they say that 'it is fair to add that the incidence in the sibs is not suggestive Doll and Buch (1950) investigated the incidence of peptic ulcer in the living sibs and parents of 300 ulcer patients and compared them with a control population An excess of ulcers was observed in the brothers sisters and father of the propositi Evidence was obtained suggesting that familial incidence was more prominent in duodenal ulcer patients and in those with early onset but the differences were not statistically significant Craig (1948b) thought that the cause which is responsible for the evolution of gastric and duodenal ulceration which has occurred during the last hundred years must be sought in environmental circumstances rather than in constitutional factors

Ivy Grossman and Bachrach (1950) considered the remarkable tendency of ulcer to recur in the same individual as crucial evidence which demonstrates the individual constitutional susceptibility of the "ulcer susceptible patient

The Editor of the *British Medical Journal* (1943) suggested that 'to separate the ulcer patient from his diathesis is like severing the fisherman from his soul and until we learn some new secret from Nature we must be content to try to teach the patient how best to live at peace with his ulcer—and to do this he must probably learn how to live at peace with himself

The occurrence of ulcer in identical twins

The occurrence of ulcer in identical twins has been suggested as supporting the hereditary factor in the familial incidence of peptic ulcer but the evidence is rather scant and unconvincing Schindler (1935) reported a detailed study of twin brothers aged 39 years who had ulcers on the lesser curvature of the stomach which perforated within one month of each other Kidd (1938)

Stenbuck (1924) thought that these individuals had characteristic facies which are usually thin and drawn with high malar prominences, are poorly nourished, are energetic in their demeanour and have an anxious expression

Hurst (1924b) suggested that there exists an inborn variation from the average normal, which manifests itself in hypertonicity of the stomach, active peristalsis, rapid evacuation, hyperchlorhydria and hypersecretion Although such a state was considered as not being incompatible with normal digestive health, it was assumed that because the greater peristaltic activity caused a flow of large quantities of highly concentrated gastric juice into the duodenal cap, especially during intervals between meals, there might be a great susceptibility to ulcer formation The inherited tendency was supported by Huddy (1927) and by McVicar (1927)

Draper (1930) pointed out that not only did patients who had an ulcer have certain anthropometric relationships, but that certain physiological factors were also characteristic of the ulcer bearing patient According to Draper and Touraine (1942) patients who have ulcer belong to families in which the long thin type of individual predominates, in contrast with patients who have disease of the gall bladder, whose families are composed of a majority of short stocky persons, that it is possible, almost without error, to determine from the individual s constitution whether the location of the ulcer is gastric or duodenal

Mattison (1931), from an investigation of 844 ulcer cases, found 443 positive and 401 negative cases of heredity involved Ryle (1932) and Wilkie (1933) believed that there is a type of individual particularly prone to ulcer and that heredity plays a part Meyer, Maskin and Necheles (1936) found that an analysis of the gastric secretion in a large group of healthy members of "ulcer families" revealed an abnormal response to the Ewald test meal and a high acidity of the resting stomach

Hurst s theory (Hurst and Stewart, 1929) that there is a hypersthenic and hyposthenic gastric diathesis which corresponds respectively to duodenal and gastric ulcer is rejected by Morley (1932) Bauer (1934) emphasized that all "endeavours to classify individuals by their 'habitus' into different types and to correlate them to dispositions to diseases have failed '

According to Riecker (1933) there was a family history of ulcer in 13 per cent of 942 patients with ulcer In 121 cases having a positive family history the familial incidence of carcinoma of the stomach was 33 per cent He found that there was a familial incidence of peptic ulcer in upwards of 30 per cent of the cases reported in the literature and believed that this strongly supported the constitutional viewpoint of the aetiology of the disease He added, however that non allergic diseases such as gallstones, rheumatic fever, cancer and diabetes also occur commonly in families

Feigenbaum and Howat (1935) observed no anatomical characteristics distinctive of patients with diabetes mellitus peptic ulcer or cholecystitis A comparison between the figures obtained by Draper (1924) and their own pointed towards agreement but opposite conclusions were reached because of the different statistical approaches Their view is supported by the observa

(1941–42), Berg (1946), and Carlson and Hoelzel (1946), protein deficiency by Hoelzel and Da Costa (1937), Weech and Page (1937), Riggs, Reinholt, Boles and Shore (1941, 1944), Kretchmar (1945), Freeman and Li (1946) vitamin A deficiency by Manville (1933), Somervell and Orr (1936–37) and Jensen (1946), vitamin B deficiency by Moore and Plymate (1932), Walldorf and Kellogg (1932), Sure and Thatcher (1933), Howes and Vivier (1936) Markoff (1943), Walters (1947), and Kiefer and McKell (1947), vitamin C deficiency by McCarrison (1931a), Smith and McConkey (1933), Archer and Graham (1936) and Hanke (1937), vitamin D deficiency by Almquist and Stockstadt (1935), pantothenic acid deficiency by Zucker Berg and Zucker (1945), and Berg, Zucker and Zucker (1949), amino acids deficiency by Weichselbaum (1935), and Co-Tui, Wright Mulholland Calvin, Barsham and Gerst (1945) vitamin E (α tocopherol) by Harris, Hove Mellott and Hickman (1947)

The food element

Sohlern (1889) who mentioned the absence of ulcer in horses, cows and other animals, drew attention to the fact that the inhabitants of Russia rarely suffered from ulcer and that they lived to a great extent on vegetable food He suggested that this may be due to a greater intake of alkali which increases its blood contents and produces a relative immunity against ulcer Friedenwald (1912) found a history of former indiscretions of diet in 43 3 per cent of 1 000 cases Westphal (1914) blamed the consumption of ice cream and iced water as a cause of the widespread incidence of ulcer in North America McCarrison (1921) who performed 3 600 operations on primitive Himalayan mountaineers found no ulcer The white race under primitive conditions appears to be less prone to ulcer Robertson and Hargis (1925) suggested that certain fundamental changes in composition, choice, preparation and manner of ingestion of food materials would prove the most plausible explanation for the increase in the incidence of duodenal ulcer

Proctor (1925) studied 1 000 case histories of gastric ulcer and 1,000 of duodenal ulcer In 16 cases of the former and 26 cases of the latter symptoms had been present in childhood Hauser (1926) refers to numerous authors (Ziemssen Leube, Heller Bamberger Decker, Haber Pierson Craemer, Ploenies) who have blamed the consumption of hot foods and drinks as the cause of ulcer in cooks Harris (1928) thought that the high carbohydrate poor vitamin diet on which the large proportion of Americans live may predispose to ulcer, though the exciting cause of the ulcer was a superimposed infection

Bergsma (1931) reported that in Abyssinia gastric and duodenal ulcer in the black people is a relatively common disease and that the diet consisted of heavy sour bread and a sauce which contained approximately 50 per cent cayenne pepper (capsicum)

Kouwenaar (1930) in post mortem examinations, found that of 1,370 Chinamen in Sumatra 151 (11 per cent) had ulcers or scars while of 1,269 Javanese men only 8 (0 63 per cent) were affected of 399 Javanese women

described perforation, in dizygotic male twins, aged 41 years, unmarried and living together in one household The first perforation occurred in the brother who was a stout man of robust appearance, the other brother, who was a thin underdeveloped man of haggard appearance, had haemorrhage and melaena on the following day and perforated 48 hours after the first one Both had apparently chronic ulcers which were situated at the junction of the first and second parts of the duodenum Riecker (1946), who refers to a case reported by Mentzingen in 1935 of twin sisters aged 20 years with roentgenographic evidence of duodenal ulcer, claimed that his own case of peptic ulcer in identical twin sisters of the same age, who married brothers, was the fourth case reported in the literature They had gastric symptoms a few months after childbirth, radiological examination showed a duodenal ulcer The father had a gastric resection a few years previously The sisters had attacks of acute appendicitis within 11 days of each other

Ivy and Flood (1950) have described the occurrence of peptic ulcer symptoms in identical twins of a family having a high incidence of peptic ulcers The father at the age of 87 years had a perforated ulcer, the oldest brother had a duodenal ulcer, the youngest brother suffered from haematemesis, one sister had an irritable duodenum, another had epigastric distress both having been operated on for appendicitis One brother had a coronary occlusion while another had no medical history Both twins developed duodenal ulcer at the age of 21 years Both had bleeding episodes, one had a gastroenterostomy followed by a subtotal resection which did not abolish the symptoms The other had a cholecystectomy for cholelithiasis which did not remove the ulcer symptoms nor prevent a recurrence of the bleeding The authors concluded that the evidence on the occurrence of peptic ulcer in families and monozygous twins supports but does not establish the view that an organ susceptibility to ulcer is inherited

Conclusion

A review of the contradictory evidence makes it difficult to accept that an ulcer diathesis, that is to say, a hereditary constitutional factor, forms the substratum on which chronic ulcer develops The author (Spira, 1931) has suggested that the single factor responsible for the familial incidence could be found in common familial food habits

FOOD IN THE CAUSATION OF ULCER

The food element as a cause of peptic ulcer may be approached from two aspects (1) the negative, due to deficiency states, and (2) the positive, which deals with the consumption of certain types of food

Deficiency states

Dietary deficiencies as a cause of ulcer were suggested by Pappenheimer and Larrimore (1924) and Sun (1926), starvation (fasting) by Hoelzel and Kleitman (1927), Bogoras (1935) Chen (1941), Morris and Lippincott

marked emaciation and inanition of the animals causing death, but did not cause any ulcerative lesions in the stomach or duodenum

Steele (1944) has suggested a theory that malnutrition due to sluggish inefficient liver action is the cause of peptic ulcer Douglas Wilson (1944) referring to the dyspeptic symptoms in the Army which often dated from youth and were unremittant and progressive, reported that this progression was attributed to greasy food

Roth and Ivy (1944c) suggested that the excessive use of caffeine-containing beverages might play a contributary role But Giddings, Wynn and Haldi (1945) concluded that the available experimental data offer no valid reason for the conclusion that the consumption of caffeine containing beverages (coffee or tea) plays a part in the pathogenesis of gastric ulcer in man

Hyman (1945), on the observation that peptic ulcer has been treated with reasonable success by the reduction and neutralization of gastric acidity correlates the considerable variations of gastric secretions with corresponding inverse variations in the level of blood cholesterols and blood lipids Since the primary function of cholesterol concerns the transportation of fatty acids in the blood plasma and bears a constant relation with fat and phospholipids, and since fat and its derivatives have an inhibitory action on gastric secretion and motility, he argues that there may be a possible relationship between cholesterol and peptic ulcer

Ivy Grossman and Bachrach (1950) state that while they do not negate the role of nutrition in the aetiology of gastric ulcer the evidence as supplied by the available autopsy statistics of the incidence is not convincing

Miscellaneous theories have been suggested but have not stood the test of time

4 (1 per cent), and of 123 Tamils 4 (4 9 per cent) were similarly affected The figures for the Chinese and Tamils correspond with those which he found in Europe In considering the influence of feeding on the striking difference in the incidence of both races employed as labourers on the plantations, Kouwenaar stated that they fed themselves in nearly the same way, but it is noteworthy that he underlines that the Chinese eat a little more meat and the Javanese a little more fish, the Chinese eat a little more fat in the form of lard while the Javanese use very little fat, generally in the form of cocoanut oil In the discussion which followed Kouwenaar's communication, Rosedale drew attention to the fact that the Chinese frequently spoiled such vegetables as they take by their habit of frying them, Given expressed the view that a simple diet of 2 chief meals a day combined with hard manual labour is the foundation of a healthy digestive system Lichtenstein observed only 2 cases of clinical gastric ulcer in 13 year of practice in Java but many cases of gastric ulcer in European soldiers who had been stationed in Java for 1–1½ years Bonne, Hartz, Klerks, Posthuma, Radsma and Tjokronegoro (1938) observed a striking difference in frequency of gastric ulcer and gastric cancer between the Malays and the Chinese in Java and Sumatra They suggested that a psychogenic factor may be involved since the absence of visible emotions is rather characteristic of the Malay race According to Brummelkamp (1933) the gastric acidity and motility in Malays is comparable to that of Europeans Bonne, Kouwenaar and Ten Seldam (1940) found 3 03 per cent incidence of duodenal ulcer in 2,237 Chinese men, 0 47 per cent in 259 Chinese women, 1 22 per cent in 3,281 Malay men and 0 54 per cent in 1,320 Malay women The incidence for gastric ulcer was 5 33 per cent in 2,362 Chinese men, 0 34 per cent in 295 Chinese women, 0 32 per cent in 4,183 Malay men and 0 52 per cent in 1,730 Malay women

Boland (1935) who reported a lower susceptibility in the Negro of Atlanta pointed out that the food of the southern Negro compares measurably with that of the native of the Himalayas, they do not consume a great amount of meat Close enquiry disclosed that the victims had strayed from the usual diet

Somervell and Orr (1936) observed that in the non ulcer area in India the main part of the diet was rice while in the ulcer area less rice was eaten Boldyreff (1938) refers to the observations of Sperck who long ago reported that inhabitants of East Siberia who subsist mainly on a very fat fish diet were frequently suffering from ulcer

Degeneration in Auerbach s plexus, accompanied by some changes in the mucosa has been consistently observed in rats and dogs fed on diets resembling those consumed by the poorer classes in Madras Presidency and Travancore, South India, by Orr and Rao (1939)

Dogra (1941) administered high spiced rice and curry diet supplemented with green foods and plantains over a period of almost 2 years to monkeys (Macaca Radiata), this caused no ulcerative lesion in either the stomach or the duodenum of the animals On the other hand rice and curry and tapioca diets administered alone, that is without the green foods, resulted in

reason why a particular single lesion becomes chronic. While the problem of the pathogenesis of chronic ulcer may, therefore, be limited to the investigation of the possible factors which may be responsible for the chronicity of the lesion rather than for its initiation it does not exclude the possibility that the factor which is responsible for the initiation of the lesion may also be responsible for its maintenance If this be so then the problem is reduced to the establishment of the aetiology of the particular variety of lesion which, for some as yet unknown reason persists and becomes chronic This, however does not detract from the consideration as developed in the section on Pathology that the acute ulcer which is encountered clinically' does not become chronic it only means that the lesion which has been observed in its chronic form has not been observed in its acute form.

THE NO ACID—NO ULCER RELATIONSHIP

Schwarz (1910) has drawn attention with his dictum no acid—no ulcer to the fact that in the absence of hydrochloric acid no ulcer can form, but it is important to recognize that this aphorism applies only to the chronic form and that the ulcers which have been observed in association with achlorhydria are invariably of the acute type Bolton (1913) has made it clear that when an acute ulcer is in the stage of formation the hydrochloric acid in the stomach contents is diminished but that extending and chronic ulcers give rise to a reflex hypersecretion of gastric juice Palmer (1926a) has confirmed that all evidence pointed to the fact that chronic ulcer does not occur in the complete absence of hydrochloric acid and that the evidence usually offered to prove that ulcer may occur in the presence of achlorhydria was found inadequate either in demonstrating the achlorhydria or establishing the presence of chronic benign ulcer or indeed in both respects

Hurst (1929a) stated that there is no evidence that an ulcer ever develops in the stomach or duodenum in the absence of free hydrochloric acid

Palmer (1940) in a large series of autopsy studies (over 1 000 cases) of patients with pernicious anaemia did not find a single case of chronic ulcer In his combined studies with Schindler Palmer (1942) had not seen an ulcer in patients with complete and persistent achlorhydria In 4 277 examinations with the flexible gastroscope Schindler conducted 69 gastroscopies in 48 patients with pernicious anaemia without encountering a single instance of the type described by Rodgers and Jones (1938)

Kalk (1945) states that the presence of hydrochloric acid is a *conditio sine qua non* in the pathogenesis of ulcer Brown (1946) has never seen an ulcer case with total achlorhydria with no free HCl in the gastric content after stimulation by histamine, an observation which was confirmed by Card (1949)

The suggestion of Boles (1951) that the adherence of the theory of no acid—no ulcer be relinquished is based on the erroneous assumption that acid is not involved in the causation of chronic ulcer because it has no role in the aetiology of acute ulcer

CHAPTER 12

THE ACID FACTOR IN THE CAUSATION OF CHRONIC PEPTIC ULCER

The observation that chronic peptic ulcer is invariably associated with increased acid values has drawn attention to the possibility that hydrochloric acid may be involved as a *primary element in ulcer formation*.

In order better to understand the role which is assumed by hydrochloric acid in the pathogenesis of peptic ulcer, it is essential to differentiate between the acute and chronic lesions.

(1) It should be noted that acute ulcer occurs in the presence of normal or diminished acid values or even in the complete absence of acid and, therefore, hydrochloric acid takes no active part in its production.

(2) Chronic ulcer is invariably associated with high acid values, therefore, hydrochloric acid is an essential element, if not in its production, at least in its maintenance.

Before investigating the factors which are involved in the causation of the chronic peptic ulcer, it is essential to make the fundamental distinction of the terrain in which the ulcer forms. It will be seen that there are two distinct categories of ulcer.

The first is concerned with the ulcers which are situated extragastrically, in an alkaline milieu, and comprises the oesophageal ulcer, Meckel's diverticulum ulcer and the anastomotic ulcer.

The second category is concerned with the ulcers which are situated intragastrically, in an acid milieu which corresponds to the ulcer bearing area and comprises the gastric and duodenal ulcers.

While it is reasonably certain that by itself hydrochloric acid is responsible for the occurrence of the oesophageal ulcer, Meckel's diverticulum ulcer and the anastomotic ulcer, that is the ulcers which are formed in the alkaline milieu, its role in the causation of the ulcer which occurs in the stomach and first part of the duodenum is more obscure, since the acid level in healthy men and in healthy dogs is high but few of the former and none of the latter develop chronic ulcers.

It has previously been pointed out that while it is relatively easy to produce experimentally an injury to the upper part of the gastro-intestinal tract, the lesion *invariably belongs to the acute variety and heals rapidly*. No method has yet been devised to prolong the existence of the acute ulcer, and whereas the acute lesions are usually multiple there is no indication to suggest the

A bleeding ulcer is frequently found in the early and acute type Perforation may occur into the abdominal or lesser peritoneal cavity, peri-oesophageal connective tissue, pericardium pleura and lungs Rarely, the aorta may become involved Perforation may cause mediastinitis, broncho-oesophageal fistula, abscess or pneumonia

According to Allison (1949) the region of ulceration of the oesophagus is immediately above the cardia but there may be a centimetre of squamous epithelium between the lower border of the ulcer and the gastric mucosa—showing similarity with the anastomotic ulcer

AETIOLOGY

Two different mechanisms have been suggested as being responsible for the production of the chronic oesophageal ulcer

The first which only applies to a small proportion of cases suggests that an aberrant gastric mucosa is present in the wall of the oesophagus secreting the acid which is the causative agent Its occurrence is rare (Taylor, 1927) Rector and Connerley (1941) in a review of the literature found 118 (11 8 per cent) in a series of 1,000 consecutive autopsies in infants and children Inflammation was frequently present Moore (1944) has emphasized that in those cases in which ectopic gastric mucosa is present the site of the ulceration is not in the aberrant gastric mucosa itself but in the adjacent tissue showing similarity with Meckel s diverticulum ulcer

The second suggestion concerns the greater majority of the cases and corresponds more closely to the anatomical findings it is that the ulceration is caused by a retrograde flow of gastric juice into the oesophagus the cardia being incompetent and failing to prevent regurgitation of the gastric secretion into the lower part of the oesophagus

According to Pringle Stewart and Teacher (1921) the chronic oesophageal ulcer is situated as a rule, in the lowest part close to the cardia In 6 of 36 cases (17 per cent) which came to autopsy it also involved the adjacent part of the stomach and the appearance of the ulcer pointed to a primary seat in the cardia with invasion of the oesophagus by direct extension The authors considered that the first requisite for the formation of the peptic ulcer of the oesophagus is an insufficiency of the cardia

Friedenwald Feldman and Zinn (1928 1929) observed in dogs that ulcers in the oesophagus produced by removal of a small section of the wall through the oesophagoscope will heal readily within a week when treated with a 10 per cent solution of hydrochloric acid they become chronic and healing will be markedly delayed Perforation is a frequent occurrence They observed a patulous cardia in 10 of 13 cases

Stewart and Hartfall (1929) agreed with Pringle Stewart and Teacher (1921) that the pathogenic factor of prime importance is the digestive action of regurgitated stomach content aided in many cases by lowered tissue vitality Chevalier Jackson (1929) reported on 21 cases and held a similar view as to the pathogenesis of the lesion

Selye (1938a) produced haemorrhagic oesophagitis by ligating the pylorus

THE ACID ULCER RELATIONSHIP

Ulcers situated in the alkaline milieu

The ulcers situated in the alkaline milieu comprise the oesophageal ulcer, Meckel s diverticulum ulcer and the anastomotic ulcer

Oesophageal ulcer

Ulcers encountered in the oesophagus are similar in type to the acute and chronic gastro duodenal ulcers, and are differentiated only in as much as they are located outside the ulcer bearing area, in the alkaline milieu Acute ulcers are met with not infrequently, but chronic ulcers are a rarity (Stewart and Hartfall, 1929)

The acute ulcer

Tileston (1906) stated that acute oesophageal ulcers occur in association with acute infective diseases and that these simple ulcers resemble closely, both in gross and microscopic appearances, the simple ulcers of the stomach Pringle, Stewart and Teacher (1921) observed 16 cases *post mortem* in 7 years (1914–21) an incidence of about 0 6 of all autopsies, 6 were associated with appendicitis, 3 with pancreatitis and gallstones and 1 with duodenal ulcer, 1 with anthrax, 1 with hepatitis, 2 with puerperal eclampsia and 2 with pneumonia, 1 each with rupture of the liver and fracture of the femur, they considered that such cases are all of a severe infective or toxic nature The condition of the oesophagus varied from superficial erosions of the mucous membrane to deep ulceration and perforation or extensive destruc tion of the tissues It is noteworthy that there was no digestion of the stomach itself and that the cardiac orifice remained closed

Masters and Bunts (1934) observed 6 cases of brain lesions which were associated with ante mortem erosions and perforations of the upper part of the gastro-intestinal tract Each of the patients was comatose for 24 hours or longer before death, and no patient was actively digesting food

It may be concluded that the acute oesophageal ulcer is in all respects similar to the acute gastro duodenal ulcer

The chronic ulcer

PATHOLOGICAL ANATOMY

Stewart and Hartfall (1929) have described the morbid anatomy of the chronic oesophageal ulcer which in all respects resembles the anastomotic ulcer

According to Feldman (1945) oesophageal ulcer may occur in any portion of the oesophagus, peptic ulcer being limited to the lower third, and occur ring usually immediately above the cardiac orifice Those that are situated high are generally produced by extension from below or by trauma, traction diverticula or tuberculosis When near the cardiac end, they rarely extend into the stomach, while ulcers in the cardia of the stomach may extend into the oesophagus

Perforation, usually fatal occurred in about 14 per cent of the reported cases (Bockus 1943)

Conclusions

It may be stated, in conclusion, that there are two mechanisms which may be accounted for in the aetiology of the oesophageal ulcer (1) the presence of an aberrant gastric mucosa in the oesophagus, and (2) the incompetence of a patent cardiac sphincter Both involve the action of the same causative agent namely, the effect of hydrochloric acid or the hydrochloric acid pepsin combination on the alkaline mucous membrane which normally cannot resist the erosive action of the acid

It is easily shown, on the one hand why the lesion produced by the intermittent regurgitation of gastric juice allows the intermittent recovery of the irritated tissues and explains the simultaneous presence of destruction and healing which is observed in oesophagitis, and on the other hand, why the persistent secretion of aberrant gastric mucosa with no means to neutralize its effect continues the relentless destruction of the surrounding alkaline tissues The re-establishment of the normal peristaltic wave abolishes the morbid process in the former case but stimulates the secretions and further adds to the damage in the latter case Furthermore the secretion of the cardiac glands which are similar to the pyloric glands affords some protection for the oesophagus in the case of regurgitation but cannot intervene with the activities of the aberrant mucosa It will be noted that in both alternatives it is the acid which is responsible for the lesion and that the difference in the progress of destruction is conditioned entirely by the time factor the action of the morbid process being intermittent in the former and more continuous in the latter

Meckel's diverticulum ulcer

The study of Meckel s diverticulum ulcer is of particular interest because the lesion is strictly localized and the incidence of primary jejunal ulcer is practically unknown (Judd 1921b Ebeling 1933, Grossman 1938)

The occurrence of Meckel s diverticulum ulcer is invariably associated with the presence of aberrant gastric mucosa in the diverticulum. Huebschmann (1913) compared Meckel s diverticulum ulcer to the gastro-jejunal ulcer following gastro-enterostomy since in both instances the ulcers occur at the junction of the gastric and intestinal mucosa The aberrant gastric mucosa is situated at the apex of the diverticulum and may line the major portion of it Schaetz (1925) found 16 6 per cent gastric mucosa in 37 diverticula The aberrant glands faithfully reproduce the structure of the gastric mucosa the fundal type of gland being the most commonly found (Taylor 1927)

According to Aschner and Karelitz (1930) the ulcers are usually chronic in type penetrating or perforating and resemble the peptic ulcers of the stomach and duodenum They present a superficial area of necrotic tissue and exudate a zone of granulation tissue and a denser more organized substratum beneath which lies the disrupted muscularis and the thickened serosa a description which conforms with the histological findings of Askanazy

in experimental animals Bockus (1943) *quotes Tileston, Hacker and* Lotheissen who called attention to cases in which peptic ulcer of the oesophagus was associated with pyloric stenosis and gastric dilatation, causing a relative *insufficiency of the cardia and allowing the continued regurgitation of* the acid secretion

The association of oesophageal ulcer with gastric and duodenal ulcer, *cardiospasm, carcinoma, hernia of the stomach through the oesophageal* opening and short oesophagus has been noted by Dick and Hurst (1942) Allison (1946) considers that the oesophageal ulcer forms when a derange*ment of the mechanism of the cardia occurs which allows the acid gastric* juice to flow back into the oesophagus Benedict and Sweet (1948) considered regurgitation as the aetiological factor in oesophagitis and benign stricture.

Wangensteen and Leven (1949) found that gastric resection dramatically improved oesophagitis even in patients with a congenitally short oesophagus Barrett (1950) suggested that the inflammatory reaction of oesophagitis is produced by the gastric reflux but the ulceration itself is an extension of the ulceration of the body of the stomach

Ferguson, Sanchez-Palomera, Sako Clatworthy, Toon and Wangensteen *(1950) have shown in various animals and in man (cadavers) that contact* of acid gastric juice with oesophageal mucosa, whether brought about by vomiting, regurgitation or by direct application, has a very prompt and devastating effect

It is of special interest—in view of the author s theory of chronic gastroduodenal ulcer formation—that Cross and Wangensteen (1951) found diges*tion and destruction of the living oesophageal mucosa in cats and dogs can* be accomplished by bile, pancreatic juice and a mixture of the two, human bile and bile salts being particularly destructive

SYMPTOMATOLOGY

The symptomatology of oesophageal ulcer and its reaction to treatment are *characteristic Pain, which is often severe and at first appears* while eating or drinking, more particularly with hard or irritating food, occurs later with almost every meal It may also be felt after eating if the patient bends forward or lies down or does anything which increases intra gastric pressure which forces the gastric content through the cardiac sphincter Excessive salivation is common, and may be interpreted as a natural attempt at neutralization and is substantially similar to the succorrhoea encountered in Reichmann s disease it may lead to aerophagy producing oesophageal spasm (aerophagie bloquee) It is significant that pain is immediately abolished by alkalies and that it is considerably relieved by mechanical means which reduce the intra gastric tension that is, sitting up stretching the arms above the head and so on, and which diminish the pressure which is exerted on the incompetent cardiac sphincter Healing of the ulcer apparently occurs in the same manner as that of an anastomotic ulcer and the complications which may be anticipated are identical Haemorrhage was noted in 53 per cent of Tileston's cases and in 23 per cent of Friedenwald s group

Perforation, usually fatal, occurred in about 14 per cent of the reported cases (Bockus 1943)

Conclusions

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(1920) for chronic ulcer The site of the ulceration is the most significant feature of the lesion Aschner and Karelitz considered it remarkable that the ulcer was usually situated at the neck of the diverticulum or in the ileum just beyond its neck In these cases the entire pouch was lined by gastric mucosa, both chief and acid cells being noted by five of the authors in the 33 cases which they review When the lesion was located near the tip or on the body of the pouch, histological study showed the ulceration to have occurred in mucosa of intestinal type adjoining a patch of heterotopic gastric mucosa Matthews and Dragstedt (1932) confirmed that Meckel's diverticulum ulcer invariably occurs adjacent to the heterotopic gastric mucosa but only involves the mucosa of the ileum

Hudson (1933) reported 7 in 13 cases, Johnston and Renner (1934) reported 46 in 48 cases Schullinger and Stout (1934) gave a detailed review of the literature, and Carlson (1937), reviewing 152 cases, found 26 7 per cent contained a variety of heterotopic tissue

That the heterotopic ga tric mucosa in these cases secretes free hydrochloric acid and pepsin may be assumed from the fact that such secretion with attendant irritation and ulceration of the surrounding skin has been amply demonstrated in recorded cases of heterotopic gastric mucosa occurring in umbilical polyps and open fistulas from the analysis of their secretion Lindau and Wulff (1931) state that both pepsin and hydrochloric acid have been detected by Tillmanns, Lexer Denuc' Rosthorn, Stone and Taylor

As observed by these investigators, this secretion clearly begins or increases synchronously with the activity of the stomach This is in accordance with experiments on transplanted fundic mucosa in the mammae of dogs where the transplant was likewise found to secrete gastric juice in connection with feeding (Ivy and Farrell, 1925) This limited situation of the lesion has been confirmed by Mason and Graham (1932), Mondor and Lamy (1933), Brown and Pemberton (1936), Cobb (1936), Thomson (1937), Fleet (1940), and Hancock (1951)

It may be concluded from the evidence that ulceration produced by the presence of aberrant gastric mucosa in Meckel s diverticulum does not take place in the aberrant gastric mucosa itself but occurs invariably in the adjacent intestinal mucosa—the alkaline milieu—which by its very nature cannot resist the corrosive action of the gastric juices

The anastomotic ulcer

The anastomotic or gastro jejunal ulcer, which occurs after surgical intervention (gastro jejunostomy and gastrectomy) for peptic ulcer is invariably situated on the intestinal side of the stoma

Boldyreff (1915) has shown that the intestinal mucous membrane does not tolerate even weak (0 15 per cent) concentrations of acid Mann and Williamson (1923) have shown that if duodenal mucosa is exposed to gastric juice without the admixture of the alkaline duodenal juices, an ulcer will form in practically every case

Konjetzny (1925) has described severe jejunitis with scattered erosions in the loop of the gastro-enterostomy which he considered to be the initial lesions before ulcer formation Occasionally the inflammatory reaction about the area of ulceration may be so severe and extensive that either an acute or subacute obstruction of the gastro-enteric stoma or the efferent loop may result

Matthews (1930–31) noted the effect of anastomosing a Pavlov pouch to an isolated loop of the lower ileum A typical ulcer developed in all instances (6 dogs) within 80 days

McMaster (1934) established that the vulnerability of the intestinal ulceration increased directly as the distance from the pylorus Anastomotic ulcers may develop following gastro-enterostomy in patients who never had an ulcer (Eusterman and Balfour 1935) According to Judd and Hoerner (1935) there is no surgical procedure uniting the stomach and jejunum which will offer a guarantee against the subsequent development of jejunal ulcer and Graham and Lewis (1935) emphasized that the incidence is higher than is usually expected

Lake (1948) has drawn attention to the absence of anastomotic ulcer after gastro-enterostomy for carcinoma of the stomach which usually contains little or no acid

Steinberg and Starr (1934) indicated experimentally that spasm of the jejunal musculature is an important factor in the aetiology of jejunal ulcer but Fauley and Ivy (1937) concluded from similar experiments that local muscular spasm was not an essential factor

Rivers and Gardner (1940) emphasized that the situation of the majority of recurring peptic ulcerations is near the site of the surgical anastomosis

Kiefer (1942) considered that the anastomotic lesion was produced by the operative changes in gastro-intestinal physiology and that it corresponds more nearly with the experimental ulcer of Mann and Williamson than does the primary ulcer in either the stomach or duodenum

According to Feldman (1945) gastro-jejunal ulcers occur chiefly at three sites on the gastric side of the anastomosis the stoma or suture line or in the efferent loop of the jejunum close to the anastomosis About 65 per cent of cases are anastomotic and 35 per cent are jejunal Gastro-jejunal ulcer nearly always implicates the stoma Ulceration is rarely seen proximal to the stoma but in some cases both sides of the stoma are involved When occurring at the suture line it may involve both the stomach and jejunum When they occur in the jejunum they are observed close to the opening on the convex side of the jejunal loop directly opposite the gastric stoma usually within one inch of the anastomosis in the efferent loop At times the ulcer is found several inches below the stoma The majority of jejunal ulcers are noted in the angle formed by the greater curvature of the stomach and the efferent loop of the jejunum the gastro jejunal angle In a very small percentage of cases the afferent loop is involved In 99 cases of jejunal ulceration Wright found 68 in the efferent loop 14 in the afferent 11 at the mesenteric border and in 6 the site was not specified

The clinical features of jejunal ulcer after partial gastrectomy do not differ from those of jejunal ulcer after gastro enterostomy The lesion is a deep, penetrating crater usually situated in the wall of the jejunum directly opposite the stoma or in the efferent limb not far from the anastomosis

Boller (1947) distinguishes between gastritis of the gastric remnant and the inflammation of the stoma which invariably follows upon gastric operations and refers to the latter as "anastomositis" which he subdivides, according to the intensity of the lesion, into anastomositis simplex, erosiva and ulcerosa

It may be stated, in conclusion, that the aetiology of the anastomotic ulcer *is relatively simple because it is produced post operatively as a sequel to* gastro enterostomy or gastrectomy Although the anatomical distortion produced by surgical intervention may not have any mechanical effect on the propulsion of the chyme from the stomach to the intestine, it alters the physiological relationship of the stomach to the small intestine, exposes the delicate mucous membrane of the intestine which, normally, has an alkaline reaction to the direct erosive action of the hydrochloric acid at its maximum concentration

Gastric acidity is never subnormal and is practically always above normal in anastomotic ulcer It is of fundamental significance that the ulcer appears invariably on the intestinal side of the stoma and that there is always a narrow margin between the ulcer and the stoma, thus showing clearly that the ulcer forms exclusively on the alkaline side of the anastomosis

ULCERS SITUATED IN THE ACID MILIEU

The action of hydrochloric acid on the mucous membrane of the ulcer bearing area will be studied from two aspects first, the effect produced by direct administration of acid, and second, the effect obtained by the indirect production of acid in the gastric mucous membrane

The direct approach

Gunsburg (1852) postulated an anomalous increase of free acid production as a direct cause in the genesis of ulcer Since then many attempts have been made to produce the lesion by the direct effect of solutions of hydrochloric acid on the gastric mucous membrane

Samelson (1879) observed that when he administered 12 5 cc of strong hydrochloric acid to starving guinea pigs and tied the cardia and pylorus, 4¾ hours later there was no change in the gastric mucosa, 20 cc after 7 hours also had no effect, 15 cc of 5 per cent HCl with pepsin after 5½ hours produced extravasations and superficial erosions, 120 cc of 5 per cent HCl and pepsin administered over 2 hours killed the animal 1 hour later Only extravasations in the fundus but not on the lesser curvature were found Ewald (1879) fed anaemic dogs with hydrochloric acid without being able to produce a gastric lesion Matthes (1893) was unable to induce a lesion of the stomach by the daily administration for 3 weeks of 350 cc of 0 56 per cent HCl in dogs in spite of the fact that a glass ring had been previously sewn to the fundus of the stomach Ruzicka (1897) injected gastric juice in

the doubly ligated stomach of frogs but only found a very superficial action on the epithelium of the mucosa

Saitta (1900) who administered 3 per cent of HCl by mouth observed multiple ulcers only when it was preceded by bilateral vagotomy Frouin (1908) attempted a surgical partial obstruction of the pyloric orifice but could not provoke gastric stasis the stomach always emptied completely When he joined the fistula of an isolated stomach to the intestine, the intestinal mucosa was digested Borszeky (1908) narrowed the pylorus and made a gastro-enterostomy in dogs to which he administered daily 30 cc of dilute hydrochloric acid Jejunal ulcers formed only in 1 of 12 dogs

Moutier (1910) isolated the stomach by ligating the cardia and the pylorus formed a gastric fistula and anastomosed the jejunum to the oesophagus The stomach was evacuated once in 24 hours Insiduous ulcers were observed which appeared to cause no pain massive haemorrhages or perforation occurred after short periods When the gastric juice was evacuated regularly and stasis prevented no ulcers formed Bolton (1910) found that ordinarily hydrochloric acid does not exercise any effect on the gastric mucous membrane in concentrations below 0 7 per cent He suggested (Bolton 1913) that hydrochloric acid in greater strength is a poison of the gastric mucous membrane and its action is precisely the same as that of sulphuric acetic and lactic acid Hydrochloric acid in the stomach content of the guinea pig is normally about 0 2 per cent, a solution of hydrochloric acid of any strength below 0 7 per cent produces no effect whatever if introduced into the fasting stomach solutions of strengths above this produce patches of necrosis and ulceration of the mucous membrane of the stomach of small animals solutions of strengths above 0 9 per cent produce a similar condition in large animals (It will be noted that the strength of the hydrochloric acid solution which was found to be destructive to the gastric mucous membrane is never encountered even in pathological conditions in man where it does not exceed 0 5 per cent) He argued that the effect of gastric juice in retarding the healing of acute gastric ulcer which he had observed suggested that in the conditions of hyperacidity and hypersecretion a still greater tendency in the same direction should be exhibited and that since hydrochloric acid is a protoplasmic poison and a hyperacid gastric juice is a more powerful destructive agent than a normal gastric juice in producing acute ulcer the continuous administration of hydrochloric acid might reproduce the condition of hyperacidity in man He therefore fed guinea pigs on food soaked with 0 5–0 6 per cent solution of hydrochloric acid but he found that the ulcers which were produced subsequently in the animals passed through exactly the same stages as those in the animals used as controls Furthermore when the animals were kept on food soaked in 4 per cent sodium bicarbonate solution the experimental ulcers passed through the same stages as the controls He concluded therefore that alterations in the acidity of the gastric content alone did not materially affect the time of healing of the ulcers

Friedman and Hamburger (1914) tied a ligature round the pylorus in order to produce partial pyloric obstruction which they thought would then

lead to hyperchlorhydria from gastric retention and the prolonged and violent action of the active gastric juice, that is, hypersecretion and hyperperistalsis would produce chronic ulcers from acute ulcerations and that such ulcers may remain unhealed if the acidity later drops to normal They observed (1) acute ulcers in which healing was simply delayed, (2) typical chronic ulcers, probably stationary, and (3) progressive chronic ulcers

Spencer, Meyer, Rehfuss and Hawk (1916) who introduced 100 cc of 0 4 per cent HCl into the human stomach, found that it was promptly neutralized Apperly (1926) who introduced 400 cc of 0 3–0 35 per cent HCl observed a similar effect

Greggio (1916) after tying the pyloric artery and removing part of the mucous membrane of the stomach found that the administration of a weak solution of hydrochloric acid did not retard cicatrization, and considered that it is impossible in this way to produce a chronic lesion or any lesion which in any way resembles that of chronic ulcer

Dragstedt (1917) produced ulcers by the local injection of a 5 per cent solution of silver nitrate by a technique similar to that employed by Friedman and Hamburger (1914), while at all times there was a quantity of active gastric juice in the pouch, nevertheless, the average time required for healing was 8 days and 9 days when there was a maximum drainage for gastric juice, duodenal ulcer required 20 days for healing both in the presence and absence of acid chyme Bacteriological examination of the ulcer showed various infective organisms, the infection originating from the alimentary tract Dragstedt concluded that the digestive activity of the gastric juice is not the important factor in the delayed healing of acute ulcers of the stomach and duodenum and the consequent formation of chronic ulcers Subsequent contributions by the same author, to which reference will be made later support a diametrically opposite view

Ivy and Oyama (1921) observed that perfusion of a pouch of the pyloric antrum with 0 1 N HCl had no effect

According to Winkelbauer and Starlinger (1926) hydrochloric acid is necessary for the causation of a peptic ulcer it cannot be considered as a genetic factor but only as a conditional due A similar view was expressed by Hauser (1926)

Gallagher (1928) observed the effects of acid and trauma on jejunal transplants to the stomach Chronic ulcers were observed in 2 transplants of 17 animals (dogs) The longest observation was 154 days Attempts at artificial acidity failed to increase the occurrence of chronic ulcer in the stomach itself, in the scar tissue of the transplant or the transplant itself In 7 animals 200–225 cc of 0 22, 0 29 or 0 62 per cent solution of hydrochloric acid was administered once or twice daily There was frequent vomiting and delay in gastric evacuation Acute ulcers were observed in the gastric mucosa of 2 animals and a chronic ulcer in the fundus of one which was ascribed to the repeated trauma from the stomach tube The most constant observations were acute and chronic gastritis and multiple erosions

McCann (1929c) stated that under the mechanical conditions of his

experiments the gastric mucosa did not ulcerate from exposure to the normal autolytic action of the juice for normal periods of time Even traumatic lesions in all parts of the mucosa healed when exposed to acid pepsin for the normal periods of digestion

Gottschlich (1930) observed that solutions of hydrochloric acid of 0 8–1 5 per cent introduced into the stomach of starving cats produced superficial necrosis which disappeared after 24–36 hours, but left a chronic gastritis

Sham feeding (Silberman, 1927, Brenckmann and White 1929, Buchner and Schneider, 1931) produces multiple acute lesions of the stomach and duodenum Puhl and Brodersen (1931) emphasized that the acute inflammatory lesions obtained after sham feeding can be interpreted as produced by a toxic factor because of the severe nutritional disturbances caused by hunger In any case this type of gastritis does not correspond to the gastritis associated with chronic ulcer in man Puhl (1932) found in the sham fed animals all stages of fatty degenertion of the pyloric and the duodenal mucosa which may be produced by hunger or the inactivity of the cells or may even be a defence reaction against the irritant action of gastric juice

Buechner (1931) claimed to have produced an acute erosive gastritis by pouring 0 8–1 5 per cent hydrochloric acid into the stomach of cats Overgaard (1931) gave 350–400 cc of 0 5 per cent HCl once or twice daily to starving dogs for periods up to 4½ months, he could only produce an acute superficial gastritis but no ulceration Matthews and Dragstedt (1932) sham fed dogs for one month without producing ulcers When they isolated the stomach and duodenum by anastomosing the distal end of the cut jejunum to the oesophagus and the proximal end lower down in the jejunum no ulcers were seen after 70 days They nevertheless claim that their experiments on the experimental production of ulcers of Meckel s diverticulum may be interpreted as affording substantial support to the view that the chemical action of pepsin hydrochloric acid (of the concentration found in pure gastric juice) can by itself and alone produce a typical chronic progressive ulcer in the stomach duodenum jejunum ileum or colon [But can it be claimed as they do that the ulcers occurring in the acid ulcer bearing area that is the stomach and duodenal cap can be compared to ulcers produced in the alkaline area of the jejunum ileum or colon?] Orator (1932) pointed out that a Pavlov pouch represented a sham fed stomach—no ulcers formed in this type of pouch because it is made with the fundus which is not prone to ulceration In constructing a pouch which incorporated both the fundus and the pyloric antrum, the animals suddenly became ill and died from perforation of ulcers situated at the angle of the main pouch stomachs

Mann and Bollman (1932) found that after dilute hydrochloric acid had trickled over the inner surface of the stomach and duodenum *for a certain* length of time the defensive power of the stomach then became exhausted showing that a mechanical and not a chemical factor was involved in the production of the lesion Dragstedt (1933) *reported* a case in a youth aged 17 years with a perforating ulcer of the ileum near the entrance of a Meckel s diverticulum because it supported his view that the principal aetio-

logical agent in gastric and duodenal ulcer is the corrosive action of the gastric juice Palmer and Heinz (1934) stated that in view of their clinical, pathological and experimental observations, it is apparent that peptic ulcer occurs only in association with acid gastric juice, that the various stages from ulcerative gastritis to the formation of callous ulcer have been described anatomically, that all of these stages have been reproduced experimentally by various methods which increase the exposure of the mucosa to acid gastric chyme, and that in normal tissue acid gastric juice alone is able to initiate, maintain and extend an ulcer This brings them then, to a considera tion of the process which renders an ulcer sensitive to otherwise inadequate stimuli They claim that there is evidence that this is due to the inflamma tory process itself, even though Singer and Palmer were unable to establish a relationship between the various degrees of inflammation and the sensitivity of ulcers, and they suggest that this may have been due in part to inability to find a satisfactory means of measuring degrees of inflammation They consider that the clinical evidence of such relationship is quite definite The first symptomatic signs of subsidence of the inflammatory process and, therefore of healing should be and are a cessation of spontaneous distress followed by failure of the previously adequate stimuli to produce pain During the first few days of antacid therapy, and also during the early days of a spontaneous remission, during which time the reparative healing processes are apparently in the ascendency, the sensitivity to acid more or less rapidly diminishes, more time is required for the production of pain, and the resulting pain becomes less and less severe (Palmer, 1930) Coincidentally the epigastric soreness and the rigidity of the rectus muscle disappear Berg (1931) has shown roentgenologically that these phenomena occur long before the ulcer crater closes Palmer and Heinz (1934) consider that the acid genesis of these ulcers is perhaps most conclusively proved by the experimental production of ulcers of Meckel's diverticulum by Matthews and Dragstedt (1932) [Critical comment on these experiments has been made on a previous page]

Mann and Bollman (1935) observed that whereas the reaction of the con tents of isolated duodenum remains remarkably constant that of the intact duodenum particularly the first few centimeters, undergoes marked fluctua tions The site where duodenal ulcer develops is the chemical battle ground of the gastro intestinal tract Ochsner, Gage and Hosoi (1934) found that repeated feeding with 1 per cent solution of hydrochloric acid produced multiple acute lesions, petechiae erosions and shallow ulcers of the stomach and duodenum, as early as five days after starting the experiment After two months there was an associated gastritis and duodenitis and an increased mucous production Stevens (1935–36) introduced a cannula through the first part of the duodenum and another canula through the third part of the duodenum acid introduced through the first and recovered through the second fistula howed that the duodenum was capable of neutralizing an average of 1,800 cc of 0 5 per cent HCl in 24 hours

Howes Flood and Mullins (1936) cut (through a gastrostomy) a one sq

cm in the mucosa of the posterior wall of the antrum 1–3 cm from the pylorus and scarified the underlying muscle Instillation of 0 9 per cent of HCl delayed but did not prevent healing of the mucosal defect Acid of a concentration of 1 or greater had little or no effect upon healing Pepsin combined with the weaker concentrations of acid caused marked necrosis of the floor of the mucosal defect delayed healing but did not prevent it Tendency to chronicity was not increased The regeneration of the fibrous tissue or of the epithelium once started was not prevented by repeated insults of these solutions They concluded that the gastric juice of patients with chronic peptic ulcer has no more capacity to cause an acute mucosal ulceration to become chronic than does artificial gastric juice

Schmidt and Fogelson (1937) who repeated the experiments of Silbermann (1927) and prolonged them to 102 days observed no changes in the gastric mucosa and only minor degrees of duodenitis The administration of 300 cc of 0 36 per cent HCl raised after 10 days to 0 5 per cent HCl twice daily in addition to sham feeding 3 times daily, did not alter their results They found varying degrees of duodenitis but no gross evidence of erosions or ulcerations in spite of the fact that acid irritation was present for 10–12 hours daily over a period of 20–102 days thus confirming the results obtained by Orndorff Bergh and Ivy (1935) with histamine and pilocarpine They thought that the ulcers described by Silbermann (1927) were of a type which result from vomiting and malnutrition

Matzner and Windwer (1937) in experiments which lasted an average of 16 days and in which lesions were produced in the forestomach (rumen) of the rat found that a 1 per cent solution was equally as effective as a 20 per cent solution of pepsin with a 0 3 per cent solution of hydrochloric acid

Wangensteen Varco Hay, Walpole and Trach (1940) instilled hydrochloric acid (0 4 per cent) over an interval of 15–46 days in 4 dogs 82–108 cc per hour being allowed to run into the fasting stomach by the drip gravity method through a gastrostomy opening The instillations were made daily for 6½–7 hours No ulcers occurred Samples removed periodically for titration indicated that during the time of acid instillation an average acidity of 73 degrees of free hydrochloric acid was maintained in the stomach

Schiffrin and Warren (1942) produced an ulcer in 1 of 3 cats by introducing 30 cc of 0 1 N HCl into a gastric fistula hourly for 8 hours daily The animal was sacrificed after 8 days the other 2 after 8 and 18 days had no ulcer the latter died of acidosis When they added 3 per cent pepsin to their solution 3 of 4 cats developed an ulcer in 5–8 days and the fourth in 25 days

Wolf and Wolff (1942) watched the effect on a small erosion in the gastric mucous membrane which was subjected to the action of the patient s own gastric juice for 4 days The denuded surface increased in size and depth At the end of 4 days it measured 4 mm in diameter and presented a punched out appearance of a chronic peptic ulcer with well-defined edges and a granulating base When the lesion was protected from the gastric juice complete healing occurred in 3 days

Palmer (1942) has pointed out that from a practical point of view acute

ulcers are of little importance for they heal quickly and usually produce few or no symptoms He argued that the chronic lesion must obviously originate in a breakdown of the mucous membrane and produce a defect which proceeds to the formation of a chronic lesion Peptic ulcer occurs only in the presence of gastric juice, only in those individuals whose stomachs secrete acids and only in those portions of the digestive tract exposed to the action of gastric juice The lesion is a penetrative one, beginning in the mucosa and dependent for its extension and progression upon the ability of the gastic juice to kill and destroy living tissue It may be visualized that the acute process which is responsible for the initiation of the lesion produces its effect before the necrosis of the mucous membrane takes place, that is to say, a state which corresponds to the pre ulcerative condition and that the persis tence of this process establishes and maintains the chronic lesion

Dragstedt (1942) thought that the chemical and mechanical trauma produced by the normal gastric content, is not sufficient to cause ulcer in the normal gastric and duodenal mucosa and prevent healing or delay mate rially the healing of extensive lesions artificially produced This resistance to the digestive action of the normal gastric contents is moreover not limited to the gastric and the duodenal mucosa but also is displayed to a consider able extent by such organs as the spleen, the kidney and the pancreas

Shay, Komarov, Fels, Meranze, Gruenstein and Siplet (1945) studied the effect of the gastric juice in 87 cats After preliminary starvation they ligated the pylorus and sacrified the animal after 17–19 hours Out of 87 animals, 80 showed gastric ulceration, most prominent in the rumen, frequent in the antrum and least often in the body of the stomach—this ulceration was prevented when there was food in the stomach, but starvation alone, even after 72 hours, did not produce any recognizable lesions in the stomach mucosa Similar results were obtained in rats by Burkle de la Camp (1929)

Friesen, Baronosfsky and Wangensteen (1946) could not duplicate the results of Mann and Bollman (1932) They were unable to produce ulcer in 4 dogs by perfusing 82–108 cc per hour of 0 4 per cent HCl for 6½–7 hours during 15–46 days Cummins Grossman and Ivy (1946) gave continuous gastric perfusion of 0 1 N HCL per gastrostomy (71–83 cc per hour) which resulted in the development of duodenal or gastric ulcerations in from 50 5 to 90 hours in all of 5 dogs Severe acidosis in all of these animals was evidenced after 12 hours by vomiting and weakness Blood *p*H determina tions of 2 of the dogs were 7 14 and 7 10 after 33–52 hours respectively Four more dogs were also given 0 16 N $NaHCO_3$ by continuous drip per terminal ileostomy in addition to acid by gastrostomy and maintained normal acid base balance as judged by daily blood *p*H determinations, these animals ate well and developed no ulcers after from 59 hours to 12 days Two addition al dogs in these series were fasted, 1 showed no ulcer after 80 hours, and the second, after developing an acidosis due to inadequate introduction of base (the blood *p*H dropped to 7 25), revealed a duodenal ulcer after 54 5 hours To eliminate the possibility of regurgitation of base into the upper gastro intestinal tract 0 16 N $NaHCO_3$ was introduced by continuous drip in 3

fasted dogs receiving acid by gastrostomy, normal blood *pH* levels were maintained and no ulcers were found when sacrificed after from 74 to 77 hours They concluded that their studies showed that continuous gastric perfusion of physiological amounts of HCl will consistently produce ulceration *of the upper gastro intestinal tract in dogs and that the prevention of the* systemic acidosis which results from such acid introduction will annul the ulcerogenic effect of the acid (It will be noted that the animals display signs of acidosis—vomiting and weakness—before the ulcers are formed and that the lesions are produced by the toxaemia as indeed is shown by the fact that the establishment of the normal blood reaction prevents the occurrence of ulcer)

Stein Grossman and Ivy (1947) *observed that* (1) *primary closure* of the Heidenhain pouch resulted in acute ulcer formation with perforation in all cases, (2) secondary closure resulted in acute ulcer with perforation in 50 per cent and (3) primary closure with daily aspiration resulted in acute ulcer with perforation in 75 per cent of the cases

Bernstein (1947) commenting on experiments in his department by Matzner and Windwer (1937) on rats which had been fed and starved on *alternate days, found that hydrochloric acid in excess on the fasting days* produced ulcer lesions in 10 per cent of the rats but if pepsin was added in the same way, lesions in 85–90 per cent were produced In giving different foods the following findings appeared the rats that had fat with the pepsin and HCl developed ulcer in 70 per cent of the number used Those with glucose developed ulcer in about 50 per cent and those with protein developed it in a small percentage of cases

Fogelman, Grossman and Ivy (1949) *who used the methods of Cummins* Grossman and Ivy (1946) found that the threshold of acid concentration needed to produce ulceration lies between 0 10 N and 0 15 N when 8–10 cc per kilogram of body weight per hour are infused continuously into the stomachs of dogs for 6 days or longer and the blood *pH* is kept normal Prevention of acidosis prevents ulcer formation when 0 10 N HCl (with or without pepsin) is infused into the stomachs of dogs

James and Pickering (1949) believed that *the acid factor was operative* in duodenal ulcer but not in gastric ulcer They made 24 hour observations of the gastric acidity on 20 cases of duodenal ulcer with 23 cases of gastric ulcer and 20 controls They found that subjects with duodenal ulcer yielded more and subjects with gastric ulcer yielded less hydrochloric acid per hour than normal subjects They emphasized that the observations described in their paper provided no proof that acid is or is not a factor in the pathogenesis of ulcer but they believed that the acid hypothesis was *extremely strong* as regards duodenal ulcer but as regards gastric ulcer their observations have led *them to precisely opposite conclusions* and therefore they deduce (1) that gastric and duodenal ulcer are essentially distinct disorders and that the chief agent in their pathology is different and (2) that there is something other than intragastric acidity which is the essential agent in the pathogenesis of gastric ulcer

According to Ivy, Grossman and Bachrach (1950) the threshold of acid tolerance of the duodenal mucosa is unusually high, as indicated by the fact that from 1,800 to 2,400 cc of 0 1 N (0 36 per cent) HCl may be introduced daily at a steady rate for 10 days without causing an ulcer, provided an acidosis does not result The fact that the ulcer occurs in a circumscribed area shows unequivocally that the factor of a localized area of lowered resistance plays a role so that a minimum of two factors constantly exist in aetiological considerations of peptic ulcer, one is a locus minoris resistentiae and the other is acid, a view similar to the one suggested by Mathieu in 1898

Shay, Gruenstein, Siplet and Komarov (1948), who found that the pre feeding of approximately 25 per cent more hydrolyzed protein resulted in a very marked increase in the resistance of the rumen mucosa to peptic ulceration, believed that it represented a true increase in the mucosa resistance and that it is to be distinguished from the protective effect obtained with the other agents, for example antacids, which act by depressing the digestive power of the gastric juice Debray, Laumonier, Ravault, and Rousselet (1950) confirmed the role of the non buffered gastric juice in the production of the lesions but believed that vaso motor reactions explained the variations in the results which they observed

Madden and Ramsburg (1950) produced ulcerations of the fore stomach of 80 per cent of Shay rats which were starved for 24 hours pre operatively and for 18 hours post operatively, water being withheld The gastric secretion ratio was 12 5 cc, the *p*H varied from 1 1 to 1 8 Aluminium hydroxide therapy prevented ulceration Ligation of both vagi, ureters or common bile duct, produced a profound reduction in gastric juice volume and fore stomachs free of ulceration Madden, Ramsburg and Hundley (1951) confirmed these observations and expressed the view that the Shay rat is a valuable means in the study of the factors which influence the rate of secretion, and of only limited value in the study of the ulcerative process *per se*

Lambling, Bonfils, Hardouin and Hewitt (1951), who repeated the experiments of the Shay rat with some slight modifications, found that the lesions could be related to the alarm syndrome Bonfils, Hardouin, Lambling and Tremolieres (1951) found that nephrectomy, which did not affect the gastric acidity, prevented the ulceration in 5 (25 per cent) out of 20 rats, adrenalectomy, which reduced the volume and the total acidity of the gastric secretion, prevented ulceration in 8 (72 8 per cent) out of 11 rats

The indirect approach

An indirect approach to the acid factor in chronic ulcer formation has been suggested by the effect of acetylcholine and histamine

The function of acetylcholine in the production of ulcer

Orndorff, Bergh and Ivy (1935) studied 3 series of dogs of which the first group was injected with histamine every 2 hours for 60 days, the second group with pilocarpine every 2 hours for 37 days and the third group with pilocarpine and histamine every 2 hours for 50 days Although these

injections were followed by hypersecretion and hypermotility they were unable to produce chronic ulcer in dogs by exposing the mucosa of the stomach and duodenum for long periods of time to the constant activity of a gastric juice rich in acid and pepsin

Necheles, Levitzky, Kohn, Maskin and Frank (1936) following on the observation of Dale and Feldberg (1934) of the presence of increased amounts of acetylcholine in the splenic blood after stimulation of the vagi, suggest that if the stomach of the dog would show a considerable degree of vasoconstriction to small doses of acetylcholine a possible explanation of the genesis of gastritis and peptic ulcer might be entertained This belief was strengthened by the fact that the stomachs of ulcer patients frequently display permanent and increased activity, which may be due to a more continuous production in these stomachs of acetylcholine than occurs in normal stomachs (Necheles, Frank, Kaye and Rosenman 1936 b)

Necheles and Neuwelt (1938) suggested that the occurrence of acute peptic ulcer after the administration of extracts of posterior lobe of the pituitary is produced by acetylcholine as a physiological antagonist of pituitrin

Wright, Jennings, Florey and Lium (1940) state that the general conclusion appears to be justified that the gut, probably in its rich nerve plexuses, makes a relatively large quantity of acetylcholine, which is prevented from acting by the sympathetic nerves The inhibition can be overcome experimentally by the administration of eserine or by section of the appropriate sympathetic nerves

Discussing the work of Necheles and his co-workers, Babkin (1944) stated that the concentrations of acetylcholine that produce constriction of the blood vessels in the stomach of the dog or the rat are supposed to correspond to those found by Dale and Feldberg (1934)—about 27 *gamma* per cent—in the blood of the dog after 1½–2 minutes strong stimulation of the vagi In the experiments of Necheles and his co-workers larger doses produced vasodilatation Dale and Feldberg observed a marked output of acetylcholine from the stomach under vagal stimulation only when the action of the vagi threw the muscular wall into vigorous contraction but in order to obtain a secretory effect much more protracted stimulation of the vagi is required —say of 20–30 minutes duration or more Therefore argues Babkin it seems likely that in the experiments of Dale and Feldberg the acetylcholine was derived from the muscles rather than from the mucous membrane of the stomach The theory of the genesis of gastric ulcer formulated by Necheles and his associates is not compatible with the conception that histamine may be one factor in the production of this condition Histamine he believed, was liberated in the gastric mucosa by acetylcholine Would not acetylcholine if produced in unusually large amounts by the action of the vagus nerves mobilize in its turn an excess of histamine which might disturb the blood circulation in certain regions of the gastric mucosa?

Stavraky (1945) observed that acetylcholine, when injected into various branches of the gastric artery in dogs in a quiescent stomach, had a tendency

to evoke different responses from different regions of the viscus Gastric juice secreted from the lesser curvature was of low acidity but contained large quantities of mucus and pepsin An abundant flow of alkaline gastric juice was usually obtained from the greater curvature of the stomach

Kammerling, Slezak and Grossman (1951) studied the effect on acid secretion of *irrigation with acetylcholine of the gastric mucous membrane* in two dogs with Heidenahin-type vagally denervated pouches of the fundus and one dog with two pouches, a vagally denervated fundus pouch and a vagally denervated pyloric pouch They found that it initiated a small secretion of the fundic pouch or, if histamine was given, that it augmented the rate of acid secretion These effects were of small magnitude and did not occur regularly

The function of histamine in the production of ulcer *

Since it has been suggested that the presence of histamine in the stomach may play a role in the pathogenesis of ulcer, the pharmaco dynamic properties of histamine will be briefly reviewed in order to establish its biological function

THE BIOLOGICAL FUNCTION OF HISTAMINE

The significance of the biological function of histamine will be made clearer by a brief historical summary

Barger and Dale (1910) discovered in ergot the presence of a substance which had the physiological properties of beta imidazol-ethylamine Ackermann (1910) showed that it was produced by putrefaction on beef pancreas and that the *abbau* occurred either by decarboxylation or deamination Barger and Dale (1910b, 1911) established that it was a depressor constituent of the intestinal mucosa Dale and Laidlaw (1910–11) observed that it increased the tonus and exaggerated the rhythm of contraction in plain muscle (confirmed by Guggenheim and Loeffler, 1916), that it was related to shock was confirmed by Abel and Kubota (1919) who isolated histamine in crystalline form from the mucosa of the dog's stomach and small intestine Mellanby and Twort (1912) isolated from the intestinal contents the bacillus which converted histidine into histamine Roger, Rahe Fawcett and Hackett (1915) observed that the non coagulable portion of the aqueous extract of various organs contained a depressor substance which affected smooth muscle and stimulated gastric secretion (an observation made by Vincent and Sheen, 1903) Koessler and Hanke (1919) confirmed the work of Ackermann (1910) and produced histamine from histidine by *B Coli communis* Best Dale, Dudley and Thorpe (1926–27) isolated histamine and choline from alcoholic extracts of fresh liver and lung Irradiation of histidine with ultra violet rays *in vivo* and *in vitro* produces histamine (Ellinger, 1930, Bourdillon, Gaddum and Jenkins 1930) Koessler and Hanke (1924), who investigated the intermediate metabolism of amino acids, observed that a low protein

* See also Histamine and Histamine beeswax Ulcer in the chapter on Experimental Ulcer in Part II

diet produced a low excretion of the imidazole complex, while a high protein diet produced a high excretion Gerard (1922) observed a similarity between the properties of histamine and those of the fluid found above an obstruction of the small intestine in experimental animals

Histamine is present along the whole length of the digestive tract of the guinea pig (Schild, 1939) The histamine present in the gastric mucosa has been determined by Gavin McHenry and Wilson (1933), Emmelin and Kahlson (1944) and Trach, Code and Wangensteen (1944)

Douglas Feldberg Paton and Schachter (1951) determined the histamine equivalents of the different reactions and layers of the wall of the dog s digestive tract. They found that the wall of the oesophagus contains relatively little histamine, that the fundus and the corpus of the stomach wall contain considerable amounts of histamine, and about twice as much as the pyloric region, that the wall of the intestine contains large amounts of histamine, and that the values are highest in the duodenum and decrease gradually and continuously down to the rectum In all regions the greater part of the histamine comes from the mucosa (Gavin, McHenry and Wilson, 1933) The submucosa contains relatively high histamine values those of the muscularis externa are lower than that of any other layer In those parts of the digestive tract where it is possible to separate the mucosa into two layers, glandularis mucosae and muscularis mucosae, most of the histamine is usually found in the latter In the intestinal wall the muscularis mucosa alone of all layers retains a consistently high content of histamine from the duodenum to the rectum All other layers contain progressively less as the caudal end of the intestine is approached

THE PHARMACOLOGY OF HISTAMINE

In man (and also in the dog and monkey) histamine produces arteriolar dilatation in addition to capillary paralysis Subcutaneous injection in man of 0·3 mg of histamine causes general flushing of the skin and a rise in temperature of 1° or 2° C a small decline of systolic, a great fall of diastolic pressure, and a rise of pulse rate Even a dose of 0 06 mg causes flushing of the skin of the face and a rise in temperature of 0 5° C Histamine is liberated in various organs as part of the response to tissue injury In a concentration of 1 in 3,000 it produces the triple response of Lewis (1936)

Histamine contracts smooth muscle throughout the body including that of the bronchioles and intestine The role of small doses in the production of anaphylactic shock needs no emphasis and its relation to bacterial infection and bacterial toxins which produce tissue damage has been well recognized

Ivy and Javois (1924–25c) have shown that histamine leaves the gastric secretory mechanism refractory—the degree depending upon the mode of administration—and that the normal intestinal mucosa possesses the power of rendering inert relatively large quantities of histamine Cell injury by perfusion with snake venom (Feldberg and Kellaway, 1937) and staphylococcal toxin (Feldberg and Keogh, 1937) liberates histamine Increased exertion of the heart liberates an increased amount of histamine (Gaddum,

1948) Davenport (1947) found that the metabolism of the stomach is not detectably affected by histamine *According to Hallenbeck, Code and* Gregory (1947) histamine may be a final pathway for a variety of physiological mechanisms which lead to excitation of the gastric secretory cells It should also be noted that many physiological processes are affected in opposite directions by histamine and epinephrine

According to Gaddum (1951) the antihistaminics antagonize all effects of histamine except that on the gastric juice He stated that we do not know whether histamine is to be regarded as an essential part of the normal machinery without which the body would not work, or whether it is a substance which appears only as part of the response to injury, and we know that the body of the cat, for example, contains enough histamine to kill the cat, but we do not know why it does not normally do so

According to Code (1952) the histamine of blood from different species varies widely The range within the species is more restricted The concentration of histamine in the blood of rabbits in the highest (1–4 or 5 g/ml) and the lowest in dogs (up to 0 04 g/ml) In man it ranges from 0 02 to 0 8 g/ml In the blood of most species, including man, the granular series of leucocytes (myelocytes) are the histamine carriers in the blood Normally histamine is held safely within the cells of the blood so that little or none is free in the plasma to produce physiological effects

THE RELATION OF HISTAMINE TO PEPTIC ULCER

A considerable number of experiments with histamine and the histamine beeswax mixture have shown that a peptic *ulcer can be produced* by its administration, but it is essential to point out that unusually large doses of histamine were used—30 mg a day in dogs and 5 mg in guinea pigs—which are out of all proportion to the size of the animal and do not bear any relation to the amount of histamine used in gastric tests in the human, in whom 1 mg frequently produces unpleasant reactions If histamine were an active factor in the production of the chronic lesion, antihistaminics should prove of clinical benefit This, however, is not the case, nor has histaminase any effect on the gastric secretions

Intravenous administration of histaminase in dogs does not effect the gastric secretory response to a meal or an injection of histamine (Atkinson and Ivy 1934) The daily oral administration of histaminase powder for a period of 21 days had no effect upon the acidity of the gastric juice (Biguria and Canzanelli 1934) McIntosh (1938) could find no significant increase in blood histamine after feeding, nor after the injection of 1 mg subcutaneously Schiff (1938) gave 799 subcutaneous injections over 4½ years of 0 5 mg doses of histamine to one patient He gradually induced a lowering of total acidity and free hydrochloric acid and the patient developed an absolute histamine refractory achlorhydria which was followed by a relative achlorhydria

Gray and Bachrach (1940) have indicated that alcohol stimulates gastric secretion by causing the liberation of histamine and that atropine does not

abolish the secretory response to alcohol This indicates, according to Dragstedt Gray, Lawton and Ramirez (1940), that alcohol releases histamine by a different mechanism namely, *irritation* from that concerned in the release of histamine by secretagogues in food

Atkinson, Ivy and Boas (1941) and Necheles and Olson (1941) could find no significant decrease of gastric acidity, and Slutzky and Dietz (1942) did not observe any inhibitory action of histaminase, which did not prevent the development of peptic ulcers in dogs fed with cinchophen

Shimkin Zon and Crigler (1943) found that blood histamine is within normal limits in patients with gastric carcinoma and with peptic ulcer There is no relationship between blood histamine and the presence or absence of free hydrochloric acid in the stomach

It is interesting to note that Jacob and Israel (1938) suggested the administration of small doses of histamine for the cure of chronic ulcer Nakoda (1939) claimed good results from the administration of histaminase in duodenal ulcers The mechanism of ulcer pain appears to be vascular and is relieved by histamine which relaxes vascular spasm and increases splanchnic blood supply Since he obtained excellent results with daily injections of 0 2 mg of histamine phosphate he recommends prophylactic seasonal injection to prevent recurrence

Best and McHenry (1930) considered that there was no physiological basis for the clinical use of histaminase

Friesen, Baronofsky and Wangensteen (1946) observed that the anti histamine drug Benadryl fails to alter the secretory curve and also that it fails to protect against the histamine provoked ulcer

Kahlson (1948) stated that no experiments have been published which *demonstrate or even indicate that liberation from the pyloric region of excess* histamine into the blood occurs during the nervous or chemical phases of gastric secretion and he comments ' Actually it would seem rather unwise of Nature to resort for this purpose to a substance which in concentrations in the blood plasma sufficient to stimulate gastric secretion would produce a variety of other effects such as general vasodilatation increase in capillary permeability, contraction of smooth muscle and in hypersensitive persons, even headache Obviously the role of histamine in stimulating gastric secretion cannot be that of a hormone carried in the blood stream to all parts of the body

Hale and Grossman (1949) found that 3 week-old healed fundic and pyloric excisional ulcers in dogs did not break down and re ulcerate during the administration of histamine although ulcers developed in the adjacent normal mucosa of the pyloric portion of the stomach and duodenum

Ambrus, Ambrus and Harrison (19.1) stated that treatment with increasing doses of histamine decreased the gastric secretory response of guinea pigs to histamine injection Parrot Debray and Richet (1945) found in patients with peptic ulcer that the level of histamine in the blood increased suddenly and was from 4 to 30 times greater during painful periods, the blood level was however, normal during painless periods They observed

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CHAPTER 13

FACTORS PREVENTING HEALING

Cohnheim (1890) recognized that the real difficulty was to determine "the unknown something which prevents the healing of ulcer

Mann (1925a) pointed out that the same factors which produce the ulcer prevent it from healing In the absence of gastric content no ulcers will form Chemical and mechanical factors, infection and impaired local resist ance may be involved

The fact that hunger pain is abolished by alkalis suggested to Palmer Schindler and Templeton (1938) that the most effective means of promoting healing is to prevent the ulcer from coming into contact with acid gastric juice

Quigley (1942) suggested that hunger contractions through mechanical trauma to the area involved which may give rise to considerable distress in the patient with ulcer may also prevent healing of the ulcer Hunger contractions should therefore be controlled but Rogers and Hardt (1915) and Mulinos (1927) could not establish any significant difference between hunger contractions and digestive contractions and Brody, Werle, Meschan and Quigley (1940) found the motility similar during fasting and after feeding

Gill and Keele (1943) pointed out that at *p*H 2 3 peptic activity is sufficiently reduced for healing of a lesion to take place complete inactiva tion being unnecessary

Mann (1951) reiterated that the agencies responsible for producing the ulcer prevents its healing Only when the ulcer is protected from the acid gastric content to such a degree that the ever present reparative process can take place faster than the destructive process does healing occur, regardless of the initial cause of the peptic ulcer

One cannot avoid the conclusion that an active element must be involved in the delay of healing of the chronic ulcer and that only when its activity is abolished by its removal will the ulcer proceed to heal

THE FUNCTION OF THE GASTRIC MUCUS

It is generally recognized that one of the main functions of gastric mucus is its protective action of the gastric mucosa against all forms of irritation but particularly against the chemical ones Mucus mixed with gastric juice goes partly into solution and raises the digestive power An absolute or relative deficiency of gastric mucus has been suggested as a possible aetiological factor in gastro-duodenal ulcerative disease

an increase in the histamine level in the experimental ulcer produced by cinchophen They mention Lambling, Moutier and Girrault, who prescribed histamine for its therapeutic value because small doses abolish its secretory stimulating action Hetenyi (in Boller, 1954) stated that in association with Borbola and Bikich he demonstrated that the histamine content of the gastric juice in active ulcer cases is markedly diminished (under 20 γ per litre) and returns to normal in the inactive phase

Ashford, Heller and Smart (1949a) in a series of 14 experiments on 12 normal and 2 gastric ulcer subjects, found that injections of 0 54 mg of histamine caused a moderate rise in mean pepsin concentration concurrent with the rise in acid concentration and fluid volume

It should also be remembered that histamine does not give a maximal stimulus alike to the secretion of pepsin and mucus as it does to hydrochloric acid Since with chronic peptic ulcer there is an increase in the secretion of all three substances it is difficult to envisage how histamine could be implicated in its production without affecting the secretion of pepsin and mucus

that mucus has a part in the mechanism which prevents digestion of the gastric mucous membrane by its own secretion Hollander (1944b) held a similar view

Vanzant (1947) found that excessive secretion of mucus was one of the most striking and typical results of vagotomy Wolf and Wolff (1947) observed that the gastric mucosa is more easily damaged when engorged Under normal conditions it is very resistant to noxious stimuli, ipecacuanha and mustard caused no visible change in the gastric mucosa which is protected by mucus According to Wolf and Wolff (1948) gastric mucus is elaborated in increasing amounts as a response to physical and chemical stimuli as a protection against injury

Glass and Boyd (1950) who studied 60 patients with peptic ulcer and 106 controls with various gastric disorders found no evidence to indicate a deficiency of gastric mucin or its fractions in fasting secretions or after humoral or central vagal stimulation in the gastric content of patients with gastric or duodenal ulcer

Mucus appears to protect the stomach by (*a*) its presence in the surface epithelial cells (*b*) its resistance to peptic digestion (*c*) its inhibitions to peptic activity (*d*) its capacity to neutralize and buffer acid (*e*) its tendency to become more viscous with an increase in acidity and (*f*) its tendency to cover the gastric mucosa by a more or less continuous film (Hollander 1951) There is no evidence of a deficient mucus secretion in peptic ulcer cases It has been shown that the secretion of mucus is stimulated by acetic acid acetylcholine alcohol histamine insulin mechanical irritation pilocarpine sham feeding stimulation of the splanchnic nerves and the vagi (Babkin 1950)

Frazer at the 2nd International Congress of Internal Medicine London 1952 reported that rancid fat produced excessive mucus secretion

It may be stated in conclusion that in the normal stomach there is an increase of mucus in response to irritation and *per contra* it may be deduced that when there is an excess of mucus present in the stomach there is also some factor which produces irritation in the gastric mucous membrane and that the reaction may be considered as a true *réflexe de défense*

AUTO DIGESTION

(The defence mechanism)

The failure of the normal mechanism to prevent the digestion of the gastric mucous membrane by the gastric secretions has been blamed as being the primary cause of ulcer formation The earlier authors believed that the inherent vitality of living substances provided its own protection John Hunter (1772) reasoned that an animal substance when joined with the living principle could not undergo any change in its properties and the moment that it lost the living principle it became subject to the digestive powers of the stomach for if the living principle was not capable of preserving animal substances from being acted upon by the process of digestion the stomach itself would be digested Virchow (1853) suggested that when the normal

Physio-chemical properties

Mucus is secreted continuously (by the goblet cells) in the stomach duodenum and jejunum (Bücher, 1932, Babkin, 1944), and has an alkaline reaction (Babkin, 1928, Westphal and Kuckuck, 1933, Hollander and Lauber, 1948a, b) Pyloric pouches whether innervated or denervated secrete continuously without regard to feeding or starvation (Ivy and Oyama 1921) Florey and Harding (1934) confirmed this for denervated pouches and Jennings and Florey (1940) for innervated pouches

Both vagus stimulation (Vineberg, 1931, Jennings and Florey, 1940) and splanchnic stimulation (Baxter, 1934, Jennings and Florey, 1940) result in increased production of mucus, each probably from different mucous cells Gastric mucus becomes more viscous as the acidity increases (Bucher, 1932, Webster and Komarov, 1932, Miller and Dunbar, 1933) while alkalies decrease its viscosity (Bucher, 1932, Fontaine, 1932) Gastric mucus as well as mucus from other sources (bile, saliva) inhibit peptic and tryptic digestion and its activity is not destroyed by boiling (Klug, 1907)

Gastric mucus possesses some neutralizing and buffering capacity for acid One gramme of human gastric mucus will combine with 16–18 cc of 0 1 N HCl (Mahlo, 1938, Babkin, 1944)

It is resistant to peptic digestion (Schmidt, 1896, Pekelharing 1902, Carlson, 1916, Anderson and Farmer, 1934) and inhibits it (Babkin and Komarov, 1932, Bradley, 1933, Bradley and Hodges, 1934, Zaus and Fosdick, 1934, Komarov, 1935) The secretion of mucus is abundant during the secretory period following sham feeding, but following alcohol and histamine the secretions are small (Webster 1929) The acid binding properties of the mucous secretion have been shown by Mahlo and Mulli (1934) and Ihre (1938)

Pathological considerations

Irritation of the gastric mucous membrane produces much mucus in Pavlov pouches of dogs (Saito 1906 Pevsner, 1907 Kaufmann, 1908, Leriche 1932, Simpson 1934 Jennings and Florey 1940 Hollander, 1945 Hollander, Lauber and Stein 1947)

Fontaine (1932) has shown that mucus possesses different tinctorial properties according to whether it is in an acid or alkaline medium The thick glue like viscous substance dissolves in an alkaline medium Bücher (1932) warned about the effect of the Sippy treatment which reduces the viscosity of the mucus and so lowers its protective function against the action of the gastric juices Wilkinson (1932) found that mucus was absent or negligible in all samples of his cases of achylia of pernicious anaemia after stimulation by acetylcholine and histamine Ochsner Gage and Hosoi (1934) found that the gastritis and duodenitis which was produced by the repeated feeding of hydrochloric acid was invariably associated with an increased mucus production Henning and Norpoth (1934) found the administration of mucin to be beneficial in the treatment of gastric ulcer Komarov (1942a) suggested

effect on living animal and plant cells and as a corollary that auto-digestion of the stomach and intestine cannot take place Gastric mucosa cells are specialised cells adapted to the action of hydrochloric acid and similarly the hyphomycetes and blastomycetes which develop in different acids are adapted to their milieu

Weinland (1930) believed that anti pepsin exists in the gastric mucous membrane and anti trypsin in the intestine and that these anti ferments conferred an immunity on tissues against the digestive juices Klug (1907) found that gastric mucus which is always present in considerable quantity protects the mucous membrane by forming adsorption compounds with the enzymes Katzenstein (1908) found that when he introduced the jejunum a closed intestinal loop or the spleen into the stomach they were digested but duodenum or stomach in an everted fold introduced into the stomach cavity were not affected Katzenstein (1913) thought that anti pepsin was present in all tissues but more particularly in the gastric mucosa and that it was effective only in an alkaline milieu

Best (1915) suggested that the living tissues were protected by an "anti-ferment and that the gastro-intestinal mucosa elaborated a specific secretion which protected the stomach from auto-digestion Schoen and Griswold (1947) expressed similar views

Smith (1912 1913) studied morphological changes in tissues with change in environment. He found that the changes in the gall bladder following autoplastic transplantation into the gastro-intestinal tract produced hypertrophy and not atrophy of the mucosa Bolton (1913) thought that a poison of metabolic origin which circulates in the blood may be capable of initiating self-digestion and he insisted upon the principle of the initiation of self digestion by a blood poison and *if endogenous poisons are proved to produce* gastric ulcer in man it will no doubt be shown that they do this by bringing about a localized necrosis of the gastric mucous membrane or haemorrhage into it.

Dragstedt and Vaughn (1924) produced large windows in the stomach of dogs and into these defects they carefully sutured segments of duodenum jejunum ileum colon and such organs as spleen and kidney In no case were these tissues digested The exposed surfaces of the spleen and kidney were soon covered by a layer of newly formed gastric mucosa while the mucosa of the duodenal and intestinal implants remained entirely normal for periods of at least 9 months Similar observations were made by Necheles Ling and Fernando (1926–27) de Takats and Mann (1927) and Morton (1927)

Michaelis (1928) asked 'Why does not the acid pepsin containing gastric juice digest the wall of the living stomach itself? and he answered that it is virtually certain from a histological aspect that the acid and the pepsin though produced in the same gland are not produced in the same cells The mixing takes place only in the cavity of the stomach Now the superficial cell membranes which regulate the permeability of any cell seem to consist of some lipoid substance Obscure and equivocal though this term may be

circulation is impeded, the neutralization of the gastric secretion by the blood ceases and destruction of the mucous membrane occurs which ultimately leads to ulcer formation

Claude Bernard (1856), in an experiment which has become classical, showed that when the leg of a living frog was placed through a fistula inside the dog's stomach, it was digested by the gastric juice He believed that the epithelial layer is not easily acted upon by the gastric juice and that the epithelial cells are removed layer by layer while the underlying ones succeed in their place He also attached importance to the protective value of the the mucus These observations were confirmed and denied by different authors

Harley (1860) did not accept Claude Bernard's view but drew attention to the protective action of gastric mucous secretion Pavy (1863) repeated Claude Bernard's experiment with a rabbit's ear which was similarly digested He, as well as Brinton (1863) and Cohnheim (1890) supported Virchow's (1853) view Samelson (1879) observed that when he reduced the alkalinity of the blood to neutral no auto digestion of the stomach wall occurred

Schiff (1868) introduced a piece of meat into gastric juice, the effects were visible on the muscular fibres which became swollen and gelatinous but the epithelium was not affected When he scraped off the epithelium of a gastric fistula, no auto digestion took place Ewald (1879) rejected Claude Bernard's views because when he immersed the well shaved foot of a living puppy in a very effective mixture of glycerine stomach extract and hydrochloric acid at body temperature for 6 hours, it was not injured although the hind limbs were paralysed following section of the spinal cord Gaglio (1884) suggested that it was the absorption of the digestive products from the gastric mucosa by the blood and the lymph which prevented the auto digestion Frenzel (1886, 1887) observed that when he put the hind leg of a living frog into a solution of pepsin and hydrochloric acid (0 2 per cent) at a temperature of 38° C complete muscular destruction to the bone took place while a solution of HCl alone produced only slight epithelial destruction and some oedema of the tissues He drew attention to the fact that there was no auto digestion in the intestine which had alkaline secretions and allowed, therefore tryptic activity and had no further need for alkalinisation by the blood

According to Matthes (1893) the proteolytic enzymes do not destroy living tissue While pepsin does not destroy the gastric mucous membrane and trypsin does not destroy the intestinal mucous membrane they both destroy the mucous membrane of the urinary bladder

Fermi (1895) reviewed the theories advanced to support the reasons which explain the absence of auto digestion The vitalistic theory—the protection by the *vis vitalis*—failed as shown by Claude Bernard's experiments protection by mucus is rejected because the presence of mucus does not prevent post mortem digestion and also because pepsin and hydrochloric acid are secreted at a level below the mucus He also rejected Pavy's alkalization of the blood since it would be neutralized as it was secreted and there would be no free acid in the stomach He believed that proteolytic enzymes have no

and are not chitinous the enzyme does not act on the *surface membrane* is conjectural They point out that the bile salts which are surface active substances would predispose to auto-digestion yet bile salts are claimed to inhibit pepsin (Pavlov 1910 confirmed the inhibitory action of bile on pepsin) They make no reference in their book to their own observations (Grant Grossman and Ivy 1948) which showed that disintegrative changes in the gastric surface cells were found in mucosa exposed to bile for a few minutes and that Cytolysis of these cells suggests potential danger to the mucosa should suitable conditions for the action exist They reiterate their previous conclusions (Bachrach Grossman and Ivy 1946) but do not explain however, what circumstances lead to the establishment of these conditions Since the intestines are known to be digested quickly after death it is pertinent to enquire why auto-digestion does not take place in the intestine when trypsin is considerably more effective than pepsin (Peptic ulcers do not occur below the entrance of the common bile duct.)

Boles (1951) stated that there can be no doubt that hydrochloric acid is a prerequisite for the development of ulcer and that on the other hand it is inconceivable that acid in a normal environment produces ulcer

Hollander (1954) has suggested a two-components self regenerating mucous barrier which protects the mucous membrane against auto-digestion

Selye (1954) using the granuloma pouch observed in the rat that pretreatment of a well delimited connective tissue area with an irritant (such as croton oil) renders it resistant to the usual digestive effect of subsequently applied fresh homologous gastric juice This induced topical resistance of the connective tissue is abolished by severe systemic stress (such as can be caused by the combined effect of fasting and neuromuscular exhaustion) He concluded that no special protective substance of gastric origin need be invoked to explain the well known resistance of gastric ulcer areas to peptic digestion the inflammation of the exposed area being in itself sufficient to induce adequate local protection

It may be postulated in conclusion that whatever mechanism may be involved *a priori* hydrochloric acid cannot affect by itself the gastric mucous membrane for which it provides its natural environment unless it is assumed that some change takes place either in the mucous membrane or the acid which would transform a normal equilibrium into a pathological disequilibrium There is no evidence that either of these alternatives ever takes place That hydrochloric acid is a protoplasmic poison which is the cause of the digestion of organic substances which are brought into contact with it is generally accepted, but the administration of large quantities of acid fails to produce a lesion in the normal stomach as long as the mucous membrane remains intact—it may delay the healing but cannot initiate the organic defect It is inconceivable to envisage a situation in which acid because it destroys living tissue in general could normally affect the cell which is responsible for its secretion in a way which would bring about its own destruction

at least it is not a protein which may be subject to the action of pepsin So the membrane of the mucosa, being indigestible and certainly also impermeable for a molecule of such a large size as that of pepsin, will prevent the interior of the cells from being digested as long as the membrane is intact

According to Northrop (1937) pepsin and trypsin are secreted in an inactive form—they are quickly removed from solution by dead organisms They are not able to penetrate into living organisms

Horrall (1938) has pointed out that bile is very toxic to all body tissues, especially when the bile salts are concentrated The bile in the gall bladder is from 5 to 20 times more concentrated than that in the hepatic duct but, nevertheless, bile does not cause necrosis of the gall bladder

Dragstedt (1943) suggested that proteolytic enzymes release histamine from cells, and produce angiotoxic phenomena (contraction of arterioles and increased permeability of capillaries) but are not directly cytotoxic He therefore postulates that the ability of proteolytic enzymes to digest organized living tissue may be dependent upon their ability to injure cells, which in turn release histamine which impairs the blood flow locally and causes the cells to lose their relative resistance to digestion

According to Price and Lee (1946) omentum, intestine, liver, gall bladder, pancreas, spleen, kidney, lung cartilage, skin and even the gastric wall itself were subjected to gastric digestion in healthy dogs by implanting living tissues and organs in the lumen of the stomach or by ensuring prolonged surface contact with gastric secretion Virtually all the tissues and organs so tested underwent digestion The seromuscular coat of the stomach itself was not exempt from auto digestion The one tissue which seemed to be immune to ordinary digestion was gastric epithelium

Bachrach, Grossman and Ivy (1946) have reviewed the theories on the resistance of living tissue to digestion They refer (1) to Hunter's theory of the living principle , (2) Bernard's theory of the protective action of the epithelium, (3) Harley's theory of the protective action of mucus, (4) the Virchow-Pavy theory of the neutralizing and nutritive function of the blood supply, (5) Fermi s theory of the biochemical resistance of the living cell and (6) Weinland s theory of anti ferments They considered the factors concerned in the resistance of the gastro intestinal tract to digestion and studied (1) the resistance of the gastric gland, (2) the resistance of the surface epithelium, (3) the resistance of muscle cells, connective tissue, and fibroblasts, and (4) the resistance of a chronic ulcer to healing They concluded that the stomach does not digest itself when the circulation of its mucosa is adequate, when the tolerance of the cells to acid pepsin is not exceeded and when the nutritional or metabolic condition of the subject is adequate for the regeneration and proliferation of the cells of the gastric mucosa and for mucus secretion

Ivy, Grossman and Bachrach (1950) stated that it is well known that the selective permeability of the cell is one of the remarkable attributes of the living cell and that this attribute disappears with death or injury Why, in the case of those cells which are known to resist tryptic and peptic digestion

presence of a secondary infection in the stomach and duodenum usually by the green streptococcus

The three most important factors in the problem of the pathogenesis of peptic ulcer are according to Winkelstein (1942) (1) the mechanical factor (2) the acid factor, and (3) the tissue susceptibility

Kalk (1945) suggested that since a chronic ulcer is produced by lack of healing and an acute ulcer heals rapidly a second factor must be involved in its chronicity and that it can only be constitutional in origin

Oliver (1947) thought that the results of his experiments on Mann Williamson dogs suggested that there is another factor besides acid in the formation of ulcer in man Appleby (1948) considers that once the ulcer is soundly established and indurated, free hydrochloric acid is not the sole nor possibly the main cause of its persistence

Necheles (1949) believes that a devitalized area must exist, before digestion of the stomach by its own secretion can occur The most plausible explanation of the cause of the breakdown of resistance he ascribes to vascular changes in the stomach James and Pickering (1949) argued that even if there is an agent in the gastric juice which is concerned in the pathogenesis of ulcer it is unlikely that it is the only operative factor and it must be inferred that most of the mucous membrane exposed to the gastric juice is resistant to it

A *locus minoris resistantiae* (an area of reduced resistance) has been invoked by many authors as an additional factor which together with the excess of hydrochloric acid is responsible for the production of ulcer Ivy Grossman and Bachrach (1950) say that 'Logically the two factors cannot be separated This passive acceptance of the injury however only evades the real difficulty because the diminished local resistance can only be the *result* of some *active* process It is only when it disappears that the ulcer heals No suggestion has as yet been made to explain the reason for its disappearance and why it comes and goes

(According to Moon (1938) *locus minoris resistentiae* is the erudite term under which our predecessors recorded this observation and concealed their ignorance of the essential mechanisms involved)

It may be stated, in conclusion that there is a concensus of opinion that two factors are concerned in the causation of the chronic lesion (1) the primary factor which is responsible for the initial trauma and which persists to inflict injury to the mucosa and (2) the secondary or acid factor which interferes with the normal healing process The problem of the causation of chronic ulcer resolves itself then into discovering the irritating substance which inflicts the damage to the gastric mucous membrane continues its action and *ipso facto* gives rise to the initial reactions which represent the syndrome of hyperfunction.

THE "LOCUS MINORIS RESISTENTIAE

(THE NEED OF A SECOND FACTOR IN THE CAUSATION OF THE CHRONIC ULCER)

It has been previously suggested in respect of the chronic peptic ulcer which occurs in the acid secreting area that *a priori* hydrochloric acid or the hydrochloric acid pepsin mixture cannot by itself produce a lesion, since it constitutes the element of its normal environment, but since hydrochloric acid plays an essential part in the persistence of the ulcer, it is reasonable to deduce that a second factor must be involved in its causation

Korczynski and Jaworski (1891) regarded a permanent hypersecretion as an essential factor, but with, in addition, some inflammation of the gastric mucous membrane Ewald (1893) referring to ulcerations which follow trauma suggested that a second element (Zweites Moment) must be involved in its causation Mathieu (1898) suggested that there are two factors concerned in the production of ulcer, the reduced vitality of the tissues which allows the second factor, strong acid, to exert its destructive action Riegel (1903) considered that some defect of the mucous membrane had also to be present Bolton (1913) has suggested that the chronicity of the ulcer is dependent on some secondary factor, such as infection of the crater and margins Carlson (1923) emphasized that the gastric juice—in normal or greater than normal quantities—can itself produce anatomical or functional disorders only when it acts on tissues or mechanisms that are already pathological Emery and Monroe (1929) considered that it would appear easier to explain many of the characteristics of the disease by a fluctuation in resistance of the mucous membrane than by a destructive effect of the gastric juice A second factor was postulated by Mattison (1931) (1) the endogenous constitutional or inherited and (2) the exogenous, acquired or influenced by external factors Alvarez (1932) considered that hyperacidity is not the sole factor in the production of the disease and that it was significant that the various experimental gastric pouches failed to show spontaneous ulceration Orndorff, Bergh and Ivy (1935) concluded that some other factor besides acid is necessary for the production of chronic ulcer in the dog Ochsner, Gage and Hosoi (1936) suggested that, in addition to tissue susceptibility and constitutional predisposition the precipitating or controllable factors were (1) hypersecretion, (2) hyperacidity (3) focal infections and (4) gastric trauma Emery and Rutherford (1938–39) believed that the cause of ulcer is not acid but like cirrhosis of the liver, must be due to a sensitization of the gastric cells by something since all their experimental work shows first cell death and then digestion and erosion by acid

DeBakey (1940) reiterated his support of the views of Ochsner Gage and Hosoi (1936) According to Stein (1942) the co operation of other factors besides the acid factor is evident in both the experimental and the human ulcers According to Quigley (1942) three factors are concerned in the formation and development of ulcer (1) the existence of a specific ulcer gastritis (2) the presence of free hydrochloric acid in the stomach, and (3) the

does not occur in the normal stomach and ulcer is a stage in the inflammatory disease of the gastric mucous membrane Chevallier (1936) who made 1,000 gastroscopic examinations came to the conclusion that the distribution of the gastritis indicates to the surgeon the extent of the inflammation and conditions the prognosis According to Orr and Rao (1939) inflammatory changes were noted in patients with subjective symptoms of ulcer in whom no ulcer was found at operation

HYPERSECRETION

Bolton (1913) explained that hypercholrhydria means that the gastric juice contains a percentage of hydrochloric acid which is greater than normal In these cases it is considered that the disorder of secretion is a primary condition and that it produces certain abnormal changes in the digestive processes which result in the form of indigestion known as hyperchlorhydria There is no doubt that the condition of the gastric secretion is merely a phenomenon in the course of the disease and not the cause of the latter According to Carlson (1915) there is no evidence that the gastric glands under any pathological condition are able to, or do secrete a juice of higher than normal acidity

A similar interpretation applies to the pepsin variations Butcher (1925–26) found that his own curve of secretion of pepsin corresponded in shape to the curve of the free hydrochloric acid Vanzant Osterberg Alvarez and Rivers (1936–37) observed that in cases of duodenal ulcer the concentration of pepsin was considerably higher than normal and it varied with the severity of the symptoms of the disease and with the degree of acuteness of the inflammatory process

Doll Jones and MacLagan (1949) investigated the subsequent digestive histories of 85 healthy men who had a histamine test meal performed 15 years previously 10 who had developed symptoms suggestive of peptic ulcer showed an average volume of gastric juice significantly higher than the remainder they therefore concluded that hypersecretion is a cause rather than an effect of peptic ulcer

Glass and Boyd (1950) found that the output of gastric mucoprotein was increased significantly in patients with duodenal ulcer as compared to controls and to patients with gastric ulcer after central stimulation as well as in the fasting stomach They conclude that since this substance forms in the mucoid cells of the gastric glands this observation fits into the general pattern of hyperactivity of gastric glands in patients with duodenal ulcer and accompanies the greatly increased output of HCl and the augmented volume of secretion in the disease The evidence indicates also that hyperacidity in the stomach of patients with duodenal ulcer is due only to increased volume of HCl secreted rather than to any primary disturbance of the buffering mechanism of the stomach provoked by deficient secretion of gastric mucin

The phenomenon hyperchlorhydria may be considered as being identical with hypersecretion in which the acid itself has not undergone any patholo

CHAPTER 14

THE SYNDROME OF HYPERFUNCTION

According to Loewi (1934) the characteristic of all living tissue is its ability to react to a stimulus, which is defined only by its effect Whether the stimulus be of a chemical, physical or a mechanical nature, it produces a specific change of energy in living tissue and from this alone results the specific function of the cell, the cell complexes, and the organs respectively Lubarsch (1923) has emphasized that passive manifestations are only those related to the rapid extinction of life As long as the cell is alive and not completely paralysed, it still reacts but with a changed energy condition

HYPERAEMIA

It has been shown (Heyrovsky, 1913, Moskowitz, 1922 Puhl, 1926, Kirklin, 1929, Welbrock, 1930 Konjetzny, 1930, Aschner and Grossman, 1932, and Faber, 1935) that gastritis and duodenitis are constantly associated with ulcer, and that by themselves they may produce ulcer symptoms Various stages of transition from gastritis to ulcer have been demonstrated Schoemaeker (1925) reported on 45 cases of the red stomach' as described by Moynihan (1921) He confirmed the dark red colour of the hyperaemic pyloric antrum which usually passed to the duodenum, the fundus and body were not red The patients had all the subjective symptoms of peptic ulcer Konjetzny (1925) conceived ulcer genesis as the continuation of an initial inflammatory destructive process of the gastric and duodenal mucous membrane He claimed that these ulcerative lesions cannot be distinguished from any other ulcers which follow inflammatory processes and that the conception of a simple corrosive or peptic ulcer devoid of reaction cannot be sustained Konjetzny and Puhl (1927) believed that the same inciting agent is present in both these lesions

Konjetzny (1930) emphasized that the inflammatory reaction may be produced not only by exogenous but also by endogenous causes and he thinks that the ulcer must be considered as a complication of gastritis and duodenitis and therefore the aetiology of ulcer must correspond to the aetiology of gastritis According to Leriche (1931) the hyperaemia conditions the hyper secretion and the hypermotility Kellogg (1933) stated that an inflammatory reaction is associated with the formation of all ulcers either as a predisposing cause or as a complication

According to Aschner (1937–38), both clinically and pathologically ulcer

of the disease Since it has an identical symptomatology in the absence of a demonstrable lesion it is reasonable to suggest that the syndrome of hyperfunction which is a normal response to a persistent but exaggerated stimulus precedes the pre ulcerative stage in the development of the chronic ulcer

THE RELATION OF THE CHRONIC PEPTIC ULCER SYNDROME TO OTHER PATHOLOGICAL CONDITIONS OF THE GUT

The relation of the *acute* ulcer as a secondary manifestation of the remote, primary *acute* and *chronic* lesions has been examined in the section of Pathology The relationship of the *chronic* ulcer syndrome as a secondary manifestation of the remote primary *chronic* lesion will now be investigated

Moynihan (1910) and Paterson (1910) have found hypersecretion, hypermotility and pyloric spasm present in appendix dyspepsia Rossle (1912) reported 78 cases of gastro-duodenal disease of which 28 were associated with a diseased appendix and 28 with other pathological sources related to inflammatory disease Aaron (1915) noted that pressure on the appendix caused pyloric spasm and epigastric pain Hart (1918) observed that 23 per cent of gastric and duodenal ulcers examined post mortem were associated with cholelithiasis Barber and Stewart (1920) observed in the dog contraction of the stomach from stimulation of the appendix the gall bladder and the duodenum (confirmed by Carlson Pearcy and Boyd, 1922)

As previously mentioned in the section on Pathology Braithwaite (1923) has shown the association of the chronically inflamed appendix to the stomach through direct transmission by the lymph channels Hartmann and Rivers (1929) reported chronic appendicitis to be present in 35 7 per cent of gastric and 44 4 per cent of duodenal ulcer patients Larimore (1930) noted that 18 per cent of his cases had had appendicectomies Rivers and Mason (1931) found 16 3 per cent of cases associated with gall bladder disease in 700 surgically verified duodenal ulcers and 7 8 per cent of cases associated with 435 gastric ulcers Smithies (1934) found in 500 cases of gastric ulcer that 180 (36 per cent) had a previous appendicectomy or a laparotomy for ulcer which disclosed a diseased appendix and 70 cases (14 per cent) which were associated with cholecystitis or cholelithiasis Smith, Paul and Fowler (1931) investigated the epigastric distress associated with an irritable colon and chronic appendicitis They had observed that the introduction of a few drops of croton oil in the proximal colon was usually followed by an increase in tone and a striking increase in the peristaltic action particularly of the pyloric portion of the stomach When the irritation was confined to the appendix or applied to the mucosa of the gall bladder the same gastric phenomenon was observed In each instance the stimulating effect on the stomach was promptly abolished by atropine They also produced epigastric distress by injecting air into the colon through a rectal tube or by massaging an irritable section of the colon particularly the ileo-caecal region The pain corresponded to the changes in tone or the passage of a

gical change and in which the increase of secretion must be interpreted as a normal response to an abnormal stimulus

HYPERMOTILITY

Hypermotility of the stomach is invariably present in the early stages of chronic peptic ulcer, gall bladder and appendix (Barber and Stewart, 1919–20), but may also be associated with other lesions of the gastro-intestinal tract and anxiety complexes Ivy (1920) thought that the fundamental cause of the gastric hypermotility and delayed *emptying of the stomach in duodenal ulcer is intrinsic and is enhanced by the presence of the extrinsic nervous mechanism* Electric stimulation of the vagi near the cardia in dogs produces, according to Stahnke (1924), first hypermotility, followed by pylorospasm, chronic gastritis and ultimately erosions Duodenitis, according to Kirklin (1929), is characterized roentgenologically by marked irritability of the bulb which tends to empty itself quickly but incompletely

Todd (1930) reported that students may have hyperactive tracts for several years without developing ulcer, but hyperactivity was evident in those of his students who later developed the symptoms of ulcer Buckstein (1930) has suggested that hyperperistalsis may be one of the early phenomena produced in order to compensate for the pyloric obstruction

Shay, Gershon Cohen and Fels (1942a) believed that the failure of a duodenal *mechanism to react with the acid gastric juice, and thus to effect a normal control of gastric secretion and motility, is the cause of the abnormal gastric* motility and secretion often seen in patients with duodenal ulcer Golden (1945) expressed the view that abnormal motility may be of more physiological significance than would seem to be inherent in a mere mechanical disorder or of transit time or calibre of the lumen of the intestine Alvarez (1940) has pointed out that, theoretically, duodenal ulceration should delay the progress of material coming down from the stomach, and if severe enough it might even reverse the gastric waves but one would also expect it to increase the irritability and tonus of the stomach and upper end of the bowel and with this there ought to be a steeper intestinal gradient and a tendency to diarrhoea

This paradox, however, may easily be resolved if reference be made to the normal function of the pyloric sphincter The rapid evacuation is obviously an attempt at getting rid of a gastric irritant and the pylorospasm an exaggerated physiological response to the same irritant, it represents a true "réflexe de défense' The rapid evacuation in association with pylorospasm shows that there is no obstruction to the outflow of the gastric contents It must be interpreted as an exaggerated response of a physiological function and constitutes the *mechanism* which attempts the prevention of intestinal reflux into the stomach and thus *conforms* to the law of isoperistalsis and the function of the alimentary *sphincters* as previously postulated

It is generally accepted that the triad—hyperaemia hypersecretion and hypermotility—which constitutes the syndrome of hyperfunction is invariably present with chronic ulcer and may be recognized in the initial stages

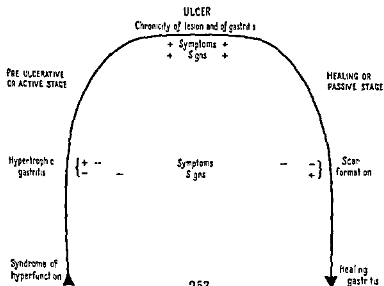
CHAPTER 15

THE CLINICAL EVOLUTION OF THE CHRONIC ULCER

Many suggestions have been made in an attempt to explain the evolution of the chronic peptic ulcer but none has so far succeeded in reconciling the apparent paradoxes of its symptom complex It will be helpful therefore, to visualize the evolution of the lesion in relation to its clinical behaviour

THE AUTHOR S DIAGRAMMATIC REPRESENTATION

The development of the chronic peptic ulcer may be represented diagrammatically by a curve in which the ascending limb corresponds to the preulcerative stage, the patient complains of symptoms but examination does not disclose any signs (symptoms are positive signs are negative), the disease becomes more apparent when inflammation is established, when the mucous membrane finally breaks down it produces the ulcer which gradually penetrates the layers of the wall of the organ This stage may be represented by a plateau which shows the persistence of the ulcerative process (symptoms are positive signs are positive) When the ulcer begins to heal, the symptoms tend to disappear but the ulcer itself is still present This stage may be represented by the descending limb of the curve (symptoms are negative signs are positive)



peristaltic wave It may occur immediately after meals or at irregular intervals but frequently a definite periodicity is observed which corresponds to the appearance of hunger contractions They considered that the pain was induced by reflex stimulation of the stomach and was due to pylorospasm Kobro (quoted by Nedzel, 1943) thinks that chronic dyspepsia is a forerunner of gastric ulcer Constipation, colitis, primary chronic appendicitis, different phases of chronic dyspepsia, gastritis and peptic ulcer—all these he considers as different stages and anatomical localisations of the same pathological conditions

Barron, Curtis and Lauer (1937) studied the influence of laparotomy on the gastric motor mechanism by the balloon and kymograph method in 7 patients They observed that (1) there was a tendency toward hypermotility of the stomach in patients with untreated cholecystitis associated with cholelithiasis, (2) continuous gastric motility was associated with occasional severe contractions during biliary colic, and (3) increased gastric hyper motility persisted for from 2 to 3 weeks after cholecystectomy

Brodin (1941) found that the pathological appendix produced an arrest of the barium meal in the genu inferius of the duodenum when the appendix was compressed in the erect position The observations of Clark and Shapiro (1941) relate to three cases of acute appendicitis in which pain was not the first symptom, but was preceded by nausea, therefore vomiting and malaise are rightly considered as of diagnostic importance by these authors

The pain of acute inflammation of the appendix, which is sudden, is generally followed after a lapse of a few hours by nausea and vomiting This long time interval indicates that the nausea and vomiting are not reflex phenomena The localised inflammation obstructs the progression of normal peristalsis and gives rise to retroperistaltic waves On reaching the stomach they produce the sensation of nausea and may induce vomiting

Ask Upmark (1940) found 9 instances of chronic peptic ulcer in 22 necropsies of hepatic cirrhosis

Thiessen (1941) found that clinically about 25 per cent of patients with duodenal ulcer have associated biliary disease suggesting that contiguous inflammation of the sphincter ampulla is the possible inciting agent

Hillemand and Sonea (1948) investigated the radiological association of megacolon with peptic ulcer It was observed in 172 (20 6 per cent) of 832 ulcer patients, in 16 (10 3 per cent) of 151 patients with cholecystitis in 15 (15 8 per cent) of patients with gastritis and in 9 (7 3 per cent) of 123 dyspeptics without demonstrative lesion

It should be noted that the relation between the acute appendix and the acute ulcer is metastatic and that the relation between the chronic appendix and the chronic ulcer is mechanical

Ivy, Grossman and Bachrach (1950, p 633) reasoned that appendicitis or cholecytitis cannot have a specific aetiological relation to duodenal or gastric ulcer because ulcer in both sites may develop after appendectomy or cholecystectomy, an argument which cannot be sustained

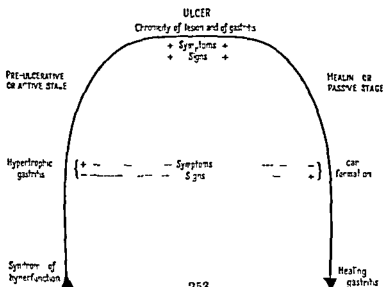
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Many suggestions have been made in an attempt to explain the evolution of the chronic peptic ulcer but none has so far succeeded in reconciling the apparent paradoxes of its symptom complex. It will be helpful, therefore to visualize the evolution of the lesion in relation to its clinical behaviour

THE AUTHOR S DIAGRAMMATIC REPRESENTATION

The development of the chronic peptic ulcer may be represented diagrammatically by a curve in which the ascending limb corresponds to the pre-ulcerative stage the patient complains of symptoms but examination does not disclose any signs (symptoms are positive signs are negative), the disease becomes more apparent when inflammation is established, when the mucous membrane finally breaks down it produces the ulcer which gradually penetrates the layers of the wall of the organ This stage may be represented by a plateau which shows the persistence of the ulcerative process (symptoms are positive signs are positive) When the ulcer begins to heal the symptoms tend to disappear but the ulcer itself is still present This stage may be represented by the descending limb of the curve (symptoms are negative signs are positive)



It will be noted that the suggested representation contains an apparent paradox in as much as the initial gastritis is associated with pain when the morbid process is active, whilst the terminal gastritis is painless when the morbid process has ceased its activity But this phenomenon, which corresponds to clinical observations, is explained on the basis that the pain producing factor is not the gastritis but the factor which is primarily responsible for the gastritis as well as the ulcer and produces pain only during the stages of activity

It is obvious that the stages in the healing of the ulcer must be in the reverse order of its formation and that the crater will disappear before the oedema and the irritability of the structures, in that order

CHAPTER 16

THE BILE FACTOR IN THE CAUSATION OF CHRONIC ULCER

FAILURE OF DUODENAL REGURGITATION AS A POSSIBLE CAUSE OF ULCER FORMATION

Although it has been clearly shown that hydrochloric acid by itself could not produce chronic ulcer nevertheless, it has been suggested that the lesion may be caused by the pyloric sphincter preventing the duodenal secretions and bile from entering the stomach One cannot but agree with Leriche (1933) however, who rejected the contention that ulcer formation is the consequence of the suppression of Boldyreff's reflex He pointed out that it would be singular on Nature s part to force the pylorus in an opposite direction to its normal opening in order to produce a reduction of gastric acidity This would be a sheer waste of energy since Nature could have provided a gastric juice with a smaller acidity or made the entrance of the gall bladder into the stomach itself There is no evidence of the existence of a physiological determining factor to justify an alkaline reflux nor of a nervous or humoral regulation, nor of any indication of a precise moment of digestion at which refex may normally occur Furthermore, the presence of bile in the stomach produces a more rapid emptying (Pannett and Wilson 1921) and, therefore would produce a physical impediment to a retrograde movement thus establishing two mutually opposing forces

According to Maier and Grossman (1937) considerable digestive disturbance may result from complete duodenal regurgitation Schmulinski s operation—gastro jejunostomy with total intragastric regurgitation (the internal pharmacy)—has been completely abandoned as it proved to be a disastrous procedure

THE ASSOCIATION OF DUODENAL REGURGITATION WITH PEPTIC ULCER

While on the one hand there appears to be no evidence to substantiate the view that failure of duodenal regurgitation is the cause of chronic ulcer there is strong evidence on the other hand, that duodenal regurgitation is associated with the presence of ulcer

Bolton (1913) observed delayed healing of acute ulcers in 10 cats with

obstruction of the duodenum Stuber (1914) believed that the regurgitation of the pancreatic juice produced peptic ulcer Greggio (1916) who produced pyloric insufficiency in dogs found the pyloric and duodenal mucous membrane studded with small haemorrhages with enlarged pylorus and marked hyperaemia Although there was no positive evidence of a peptic ulcer after 90 days, he suggested that a longer period might give more definite results Pyloric obstruction and duodenal stasis in association with duodenal ulcer was reported by Wilkie (1921), Del Valle and Donovan (1926), Hurst and Briggs (1926), Rowlands (1926), Jones (1926), Ryle (1926), Higgins (1926), Sloan (1926), Hurst and Stewart (1929), and Redon (1931) Ulcer symptoms in association with chronic gastro mesenteric ileus were reported by Stavely (1910), Kellogg and Kellogg (1921), Devine (1921), and Miller and Brown (1925)

Pannett (1926) has pointed out that peptic ulcer occurs in those regions where intestinal juice has access to gastric juice and their interaction seems to render conditions favourable to ulcer formation

Slocumb (1927) determined experimentally the effects of partial duodenal obstruction over different periods of time With about 75 per cent of obstruction he found 12 of 16 dogs with definite ulceration of the duodenum, the ulcers healed as soon as the lumen of the duodenum became unobstructed

While Enderlen, Freudenberg and Redwitz (1923) rejected Stuber's hypothesis, Redwitz and Fuss (1928) supported it and pointed out that trypsin may exert its destructive influence on the gastric mucous membrane at a *p*H of 1 5 since trypsin is greatly activated by the presence of bile

Boldyreff (1938b) suggested that the most destructive factor in the causation of the round ulcer in the duodenum is the pancreatic juice, which is frequently regurgitated into the stomach this secretion being always accompanied by intestinal juices and bile

Thayssen (1922) drew attention to the association of constipation with ulcer Faber (1925) associated constipation with gastritis, as did Rehfuss (1929) who found that resumption of normal colon function relieved gastric symptoms Alvarez (1940) observed reverse waves in the pars pylorica and stagnation in the duodenum following experimental partial obstruction low down in the bowel

Zweig (1935) considers that in the operated stomach gastritis appears either as a symptom of the ulcer syndrome or as a consequence of a diffuse pangastritis caused by the permanent reflux of the duodenal content into the stomach This would explain the symptoms of the so-called 'gastro enterostomy disease

Boller (1947) stated that an inflammatory reaction of the gastric stump is a regular occurrence as a sequel to surgery of the stomach It first assumes the hypertrophic form which later becomes atrophic He considers that the duodenal secretions are the cause of the initiation as well as the maintenance of the gastritis

CAUSES OF THE PRESENCE OF BILE IN THE STOMACH AND ITS SIGNIFICANCE

It has been suggested in a previous section that the isoperistaltic wave is the normal mechanism which effects the propulsion of the chyme in the gastro-intestinal tract and that the reversal of the wave must be considered as a pathological manifestation Since there are moments when material is carried from the intestine into the stomach as shown by the presence of bile it will be necessary to investigate the reasons for its presence in the stomach and the effects it produces on gastric function and on the gastric mucous membrane

Beaumont (1833) observed in Alexis St. Martin that violent passion at the same time retarded the passage of gastric contents into the small bowel as it produced reflux of bile into the stomach When the use of fat or oily food had been persevered in for some time bile was generally present in the gastric fluid Whether this be a pathological phenomenon, induced by the peculiarly indigestible nature of oily food or whether it be a provision of Nature to assist the chymification of this particular kind of diet he could not say but oil appeared to be affected by the gastric juice with considerable difficulty He added that irritation of the pyloric extremity of the stomach with the end of the elastic tube or the bulb of the thermometer, generally occasions a flow of bile into this organ External agitation by kneading with the hand, on the right side over the regions of the liver and pylorus produces the same effect. It may be laid down as a general rule however, subject to the exceptions above mentioned that bile is not necessary to the chymification of food in the stomach With the exceptions that I have mentioned it is never found in the gastric cavity in a state of health and it is only in certain morbid conditions that it is found there

Boldyreff (1904) gave experimental evidence that only fats give rise to regular duodenal regurgitation definite observations having been made that this massive regurgitation consists of both bile and pancreatic secretion

Best and Cohnheim (1910d) stated that dogs refuse to eat fat and that to obviate this difficulty they used dogs with oesophagotomy and gastric fistula and excluded the psychic gastric secretion Olive oil palmitin and bacon introduced into the stomach regularly produced half an hour later a copious amount of bile in the stomach Sham feeding never produced a backflow of bile Psychic motility, when the dog ate with appetite inhibited the backflow of bile

Cathcart (1911) observed the regurgitation of bile after the administration of oil oily or fatty foods and also after irritation of the pylorus He found in dogs with fistula that the administration of sodium oleate brought about the regurgitation of bile within 2 or 3 minutes while 0·2–0·4 per cent of hydrochloric acid required a considerably longer time for it to occur

Carlson (1915) believed that at times bile may normally be in the stomach but then its presence appears to have no significance Lockwood and Chamberlin (1923) observed that the administration of 1 ounce of olive oil

before meals produced a regurgitation of bile in 80 per cent of cases According to Baird, Campbell and Hern (1924b) it is difficult to know if bile is present in the resting stomach normally or appears as the result of nausea and retching They found that where the resting juice was above the average, that is, 60 cc or more, bile was present in more than 75 per cent of their cases, but it was also sometimes present when the resting juice was very small in amount Their only definite conclusion was that bile is rather more frequently present in the resting juice in the cases of hyperchlorhydria They rejected the idea that the absence of regurgitation and bile is a cause of hyperchlorhydria because it was present more frequently in the resting juice of hyperchlorhydria than in any other group, and they emphasized that the more acid the gastric contents the more likely is bile to appear in the course of a meal They considered that the presence of bile in the stomach is not the cause of low acidity nor is absence of bile the cause of high acidity

Medes and Wright (1928) found that trypsin and bile appear independently in the fasting stomach, while trypsin was present in all cases examined, bile was present in 7 of 9 cases (78 per cent) in achylia of pernicious anaemia and 4 of 9 (44 per cent) in miscellaneous cases

Rehfuss (1929) explains the presence of bile in the stomach after the administration of fat as "an attempt at intestinal digestion in the stomach —in contradistinction to the fact that carbohydrates are never accompanied by regurgitation of bile during the digestive period—and he further observes that there seemed to be a tendency for bile to appear more often in the case of long continued digestions

Bockus, Glassmire and Bank (1931) noted gross bile in the fasting residuum in 78 (39 per cent) of 200 cases of duodenal ulcer Because they failed to recover bile from the fasting stomach with any frequency in normal individuals they attributed some significance to their findings in duodenal ulcer They confirmed the observations of Lyon, who believed that frank macroscopic biliary regurgitation into the fasting stomach suggests some functional derangement at the pylorus A decided hyperacidity was present in 74 per cent of the fasting contents containing gross bile, while 56 per cent of the fasting content without bile were hypoacid

Lake (1948) reported on a patient with a gastro enterostomy which was performed 6 years prior to a partial gastrectomy Before the second operation a fractional test meal showed high acidity, reaching 90 (0 327 per cent HCl) after 45 minutes, and during the 7 tests which were made within 2 hours bile was present in all samples After the second operation achlorhydria was present, and bile occurred only in the last test the seventh, 2 hours after ingestion of the test meal

James and Pickering (1949) observed that in 16 cases of gastric ulcer, bile was present during the period of neutrality only in 10, and frequently the fall of acidity took place several hours before bile appeared They also found that absence of bile stained samples is commonest in duodenal ulcer and that bile staining is less common in the cases of gastric ulcer which become neutral at night, than in those that remain acid

The presence of bile which is sometimes seen at the end of a normal test meal has been shown to be due to the lower pressure which occurs in the empty stomach while food is still present in the upper intestine, its presence, however is of little significance because of the weak concentration of bile at the end of a meal

EFFECT OF THE PRESENCE OF FAT IN THE STOMACH ON GASTRIC FUNCTION

The effect of fat on gastric motility

The effect of fat on the motility of the stomach has been clearly demon strated to be one of inhibition with consequent delay of gastric evacuation The retardation of gastric digestion by fats was clearly shown by Beaumont (1833) Ewald and Boas (1885–86), Lintwarev (1903) and Edelman (1906) Ewald and Boas (1885–86) suggested that fatty acids are liberated which cannot be without a deleterious influence on the stomach White bread and lard in the proportion of 1 2 produced vomiting in 30 minutes Levites (1906) found in the dog that after the administration of 100 g of fat the stomach contained 65 per cent of fat 4 hours later and 14 per cent 12 hours later A similar observation was made by Wilson Dickson and Singleton (1929) who observed in man that the stomach may contain 15–50 per cent of fat after 4½ hours Cannon (1911) observed in dogs a slower occurrence of the gastric waves when fed with fat than when fed with bread and milk mush He showed that the addition of fat to his standard opaque paste delayed the appearance of any opaque material in the duodenum for half an hour this result must indicate a direct gastric effect as it occurred before material could be detected in the duodenum Carlson (1916) observed that fat decreased the motility of the fasting stomach Lockwood and Chamberlin (1923a) found that gastric evacuation was delayed by 40 minutes when they adminis tered 1 ounce of olive oil before an Ewald test meal A similar observation was made on himself by Butcher (1925) Kalk and Disse (1924) observed that while sesame oil and fresh margarine produced a slight reduction rancid margarine produced a marked reduction of the emptying time of the stomach Lim Ivy and McCarthy (1925) demonstrated that the introduction of fat into the denervated pouches of the entire stomach diminished the motility of that organ The mechanism which is responsible for this phenomenon is discussed in detail in the chapter dealing with the hormonal control of the gastric function

Brauch (1931) has shown that the fat reflex from the duodenum does not affect the pylorus by itself but the whole stomach is inhibited Northmann and Wendt (1932) found that olive oil delayed markedly the emptying time of the stomach which was not affected by the ligation of the pancreatic duct or by total pancreatectomy Lim (1933) who produced inhibition of the movements of the stomach by injecting an extract of intestinal muscle or blood from fat fed animals concluded (Lim 1935) that the fat inhibits gastric motility of both the nervous and chemical phases of the digesting stomach

McSwiney and Spurrell (1933a), who recorded the emptying time of the stomach by the "outline" method which they described, observed that the hypertonic meals produce delay in proportion to the degree of hypertonicity and that hypotonic meals leave the stomach more rapidly than isotonic meals McSwiney and Spurrell (1935) investigated the relationship between the concentration of fat in a meal and the degree of gastric delay produced thereby and concluded from their experiments (on dogs, decerebrated cats and human subjects) that the delay increases with its concentration in the meal They also found that the rate of gastric secretion exactly paralleled the rate of gastric outflow Cerqua (1935) confirmed Pavlov s observations in dogs He found that olive oil leaves the stomach slowest (120–145 m), water quickest (13–22 m), and acid solution takes an intermediate position (59-65 m) X ray examination in animals with fistulae fully confirmed these results After splanchnotomy, emptying for water was the same but greatly reduced for acid and olive oil

Quigley and Meschan (1938) noted a marked inhibition of gastric motility after the ingestion of fats which did not result from fats restricted to the stomach but required their presence in the upper end of the small intestine Quigley and Meschan (1941) showed also that the introduction of fatty acids or soaps into the proximal intestine of fasting dogs inhibited gastric motility, but Quigley, Werle, Lygon, Read, Radzow and Meschan (1941) showed that fat in the duodenum inhibited the region and at the same time decreased or reversed the antral bulbar basal and phasic pressure gradients and that evacuation was retarded in spite of sphincter relaxation They found that fats and their digestive products inhibited the entire pyloric regions of fasting and fed animals and that gastric evacuation was retarded primarily by depressing the propulsive peristalsis of the antrum Cream in the duodenum modified pressures and motility of the sphincter region less in the fed than in the fasting animal This was due in part to the exaggerated antral pumping activity incident to gastric distension in the fed animal, for a balloon containing 500 cc of air placed in the stomach of a fasting animal produced results comparable to those noted in fed animals Dilution and flushing out of the cream by the chyme discharged into the duodenum also decreased the effect of cream in the fed animal Prevention of this effect by duodenal drainage increased the effectiveness of cream in the fed animal Annegers and Ivy (1947) found that 25 of 30 normal subjects showed a delay at 4 hours when the fat content by wet weight was increased from 6 to 8 per cent, and 27 subjects showed delayed gastric evacuation when the fat was increased from 8 to 14 per cent

Harris, Grossman and Ivy (1947) found that fat inhibits gastric motility induced by distension in both the vagally innervated and vagally denervated stomach

According to Kay (1950) beef fat if uncooked, has a depressant action on gastric function With prolonged cooking, the action becomes progressively less sedative and is eventually stimulant This change of action is associated with a fall in the iodine value of the fat Card (1941) has shown however,

that even saturated fats inhibit gastric motility and it may well be that some other factor is involved

The effect of fat on gastric secretion

It is now generally recognised that the action of fat on the gastric secretion passes through two phases, first an inhibitory stage followed by an excitatory stage

That the presence of fat in the stomach inhibits gastric secretion was observed by the early contributors on gastric disorders (Ewald 1893, Penzoldt 1893) Boldyreff (1904) reported that Pavlov, Cliggin Lobasov and Wirschubski made similar observations Cowie and Munson (1908) observed that oil given immediately before or after a test meal, did not bring about so marked a lowering of the secretion as when it is given half an hour before and they concluded that oil lowers the gastric secretion both by reflex central inhibition and by mechanical action

Pavlov (1910) administered 100 cc of olive oil through a cannula into the main stomach of a dog Half to one hour later the dog was given 400 g of meat While without the oil gastric secretion of the Pavlov pouch occurred five to ten minutes after administration of the meat, with the oil it took half an hour The amount of gastric juice collected was 3–5 cc per hour as compared with the normal 10–15 cc A corresponding result was obtained when the fat was introduced into the stomach immediately after the meal of meat Pavlov showed that the effect of fat on the secretion of gastric juice is not limited to inhibition and that secretion of gastric juice begins again at the third hour if the meal of fat be at all large This late secretion lasts a long time and furnishes a considerable quantity of juice Orbeli (1906) reported instances in dogs in which the secondary rise of secretion surpassed even the usual normal response The twofold effect of fat on gastric secretion, inhibition first, then stimulation, has been confirmed by Babkin (1928)

According to Cannon (1911) fats cause the pancreatic juice to flow but the pancreatic juice instead of diminishing the acidity of the duodenal contents increases the acidity by separating a still greater amount of fatty acid Even when dissolved in bile the fatty acids give the solution an acid reaction To this increasing acidity of the contents of the upper intestine as well as to the action of fats themselves and the weak and sluggish gastric peristalsis which they evoke may reasonably be attributed the fact that fats pass from the stomach only as fast as they are absorbed or carried into the large intestine

Okada (1915) has proved experimentally that diminution of secretion takes place during starvation that this diminution occurs sooner with carbohydrates and proteins than with fats that there is a definite increase with fats oils soap and acid but that sugar water and bicarbonate of soda have little effect

Lockwood and Chamberlin (1923a) observed that the immediate effect of administering 1 oz of olive oil before meals was a lowering effect of the high point of acidity by 12 per cent

Kalk and Disse (1924) observed in man that the administration of marga

rine or sesame oil produced only a slight reduction of gastric acidity and a shortening of the period of secretion and emptying time and early appearance of duodenal regurgitation Rancid margarine produced much more marked effects Kalk (1924–25) found that the administration of 100 cc of milk or 50 g of butter produced after a temporary lowering, a marked increase of gastric secretion and a more marked state of gastric irritation and increased tendency to reflux of the duodenal secretions

Roberts (1925) observed in man that in several instances the composition of the samples towards the end of the oil meal suggested that the contents of the stomach consisted almost entirely of gastric juice, whereas this was not noticed in the control meals This observation was confirmed by Butcher (1925) on himself, and by Rehfuss (1927) Lim, Ivy and McCarthy (1925) introduced olive oil into the intestine of a dog with an entire stomach pouch and found that the subsequent introduction of a solution of 100 mg of histamine into the stomach pouch stimulated the gastric glands to secrete In this case there was no appreciable inhibitory effect in spite of the presence of olive oil in the intestine, but when a smaller dose of histamine (50 mg) was given under similar circumstances the secretory effect was diminished by the fat Babkin (1928) reported that in dogs 100 g of lean goose meat provoked 15 2 cc of juice and 67 ferment units during 5 hours, 100 g of fat goose meat gave 22 3 cc of juice and 62 ferment units during 8 hours Feng Hou and Lim (1929) using Bickel pouch dogs observed exaggerated response in the third hour after olive oil followed by a meat meal Roberts (1931) reported similar results for the human subject

The secondary rise of the secretory gastric juice after the administration of fat has been ascribed to the action of soaps in the duodenum (Babkin, 1905, Ivy and McIlvain, 1923) Wilder and Schlutz (1929) believed that the degree of inhibition produced by the saturated fats varied with the shortness of the carbon atom chain Roberts (1931) found that the efficiency of oils inhibiting gastric secretion appears to bear some relationship to the degree of saturation of the constituent fatty acids, the less saturated oils being the more efficient There was no effect when sodium oleate was introduced into the stomach but if it was introduced into the duodenum it gave rise to higher gastric acidities He pointed out that while atropine inhibits the psychic secretion but not the chemical secretion, oil inhibits both the psychic and the chemical secretions and also the chloride secretion In cases of achlorhydria in which the test meal emptied with greatly increased rapidity, the oil delayed this process

Shay, Katz and Schloss (1932) showed that the amount of regurgitation was not significant in lowering intragastric acidity in the human stomach these experiments were confirmed by the experiments of MacLagan (1934) and the clinical studies of Teorell (1933) and Hollander (1936) Alley, Mackenzie and Webster (1934) confirmed that there are two phases in the action of fat on gastric secretion Fat inhibits chiefly the nervous phase of gastric secretion but when presented in great amounts also depresses the chemical phase as well as the effect of histamine During its inhibitory phase,

which is temporary, fat diminishes the volume the acidity and more especially the peptic power of the gastric secretion During the excitatory stage fat causes the volume of the secretion to be increased, while the acidity is only slightly lowered though the peptic power remains greatly diminished

Appell (1935) showed that most foods when placed in the jejunum will cause an increase of the secretory rate of the stomach cream and casein consistently stimulated gastric acidity and secretion to a high degree Babkin (1938) pointed out that a diet rich in fat administered over relatively long periods of time, may induce a hypersecretory condition of the gastric glands coupled with almost complete paralysis of the vagal trophic action

Alley and Babkin (1939) found that histamine phosphate elicited a copious secretion of gastric juice from a Pavlov or Armour pouch notwithstanding the inhibitory effect of previously ingested fat The volume of secretion was only a little less than in the control experiment. Under the same circumstances subcutaneous injection of pilocarpine chloride evoked a gastric secretion whose volume was not less than that of the control pilocarpine secretion

Shay Gershon Cohen and Fels (1939) by simultaneous intubation of the duodenum and the stomach showed that when olive oil was instilled directly into the duodenum beginning at a time the mouth meal was taken a very marked supression of gastric secretion resulted Total chlorides as well as free and total acid were greatly depressed After 150 minutes the secretion started to rise sharply until 345 minutes when gastric evacuation was complete thus confirming the observations of Sokolov (1904) in the dog They observed that 90 minutes after duodenal instillation of oil the subcutaneous injection of 0 8 mgm of histamine produced a sharp rise in gastric secretion in spite of the continued duodenal instillation of the oil They pointed out that duodenal instillation of hypertonic glucose solution also produces a secondary rise which could not be due to the formation of soaps and they suggested therefore that this phenomenon is due to a release of stored up secretion accumulated during the period of depression Enzyme secretion paralleled that of the acid and the chlorides showing the sharp secondary rise following the depression

Komarov and Komarov (1940) using dogs with a Pavlov pouch tried adding a small amount of fat to the test meal in single experiments or to the daily meal in prolonged experiments, with the aim of avoiding the excitatory phase of the action of fat The appearance of this phase was prevented by the use of small doses of olive oil or cod liver oil (about 1 cc per kg of body weight), introduced into the stomach a short time before a test meal of meat The volume acidity and peptic power of the gastric secretion was markedly reduced There was no appreciable increase in the volume of the secretion *in the late hours of the experiment* When similar small doses of olive oil or cod liver oil were added to a standard diet for one or two weeks, they likewise depressed the gastric secretory activity in the Pavlov pouch dogs Ivy (1941) has pointed out that after the inhibition due to fat is over the gastric secretion returns to a high rate Babkin (1944) stated that the knowledge of the mode of action of fat on gastric secretion is of practical value At one time fat was

recommended by the clinicians for the purpose of inhibiting the activity of the gastric glands in cases of hypersecretion The disadvantage of this method was that a large amount of fat (such as is prescribed in Sippy's diet, for instance) would produce during the excitatory phase a gastric secretion so copious that it might partially or perhaps entirely compensate for the inhibitory action of the fat or might even induce hypersecretion

Voegtlin (1947) showed that placing cotton seed oil or oleic acid in the stomach apparently causes the formation of gastric acid to be inhibited to a slight degree about 4–6 hours later but the effect was not sufficiently marked or prolonged Gershon Cohen (1947) showed that when olive oil is instilled at the rate of 40 drops per minute there is a marked secretory depression of all gastric secretions which is followed by a sharp secondary rise after the effect of stimulation of the duodenal mechanism wears off (fat being the most potent stimulator of the duodenal mechanism)

EFFECT OF BILE IN THE STOMACH

The effect of bile on gastric motility

Pannett and Wilson (1921) investigated in cats the effect of the addition of small quantities of bile salts (sodium taurocholate) to a standard test meal and observed a marked increase in the speed of the evacuation of the gastric content When sodium taurocholate was added to a test meal in normal men an abnormally rapid gastric evacuation took place Still and Carlson (1929) observed that the intravenous injection of bile reduced gastric motility, but this effect was produced by the toxic systemic effect and not by a local action on the organ

Winfield and Kaulbersz (1941) noted that feeding of bile relieved anorexia They observed that whole bile, or bile salts dissolved in water, when placed in a fasting dog s stomach during the quiescent phase, gastric contractions were invariably produced During the contraction phase, a short inhibition occurred Shortly after the feeding of fat (bacon or olive oil) hunger contractions ceased In only 2 of 24 experiments did the feeding of whole bile after the intake of fat call forth contractions after a resting phase produced by fat

The effect of bile on gastric secretion

Sokolov (1904) observed that bile produces an increase of gastric secretion when it is given by stomach tube or applied to the intestine, and when placed in an isolated stomach it would stimulate secretion from a Pavlov pouch These observations were confirmed by Pavlov (1910) who also confirmed the inhibitory action of bile on pepsin

Lonnquist (1906) who fed bile obtained from other animals with biliary fistulae to dogs with Pavlov pouches found that it stimulated the secretion of gastric juice to the same degree as water, but the contents of the main stomach showed almost no digestive power subsequent to the ingestion of

bile on account of the precipitation of the pepsin by bile Glaessner (1913) after feeding sodium choleate to patients with hyperchlorhydria noted a decrease in the acidity of the stomach content

Wiedemann (1914) anastomosed the gall bladder to the stomach in a dog and studied the gastric content by means of a fistula He observed occasional slight decreases as well as occasional increases to total acidity, he concluded that the acidity of the gastric content is not appreciably affected by diverting the bile into the stomach Grey (1916) by means of a cholecystogastrostomy with ligation and division of the common bile duct in dogs diverted the bile from the duodenum to the stomach The results from two series of experiments agree that bile has no appreciable effect on the acidity of the gastric content

Grey (1917) found in dogs that after ligation of the larger pancreatic duct the presence of a considerable amount of pancreatic juice in the stomach throughout the period of digestion leads only to a moderate decrease in the acidity level of the ingesta in the later stages of digestion Earlier in the process there is no constant alteration of the acidity level in either direction

Pannett and Wilson (1921) found that after the administration of bile salts to normal men there was a striking rise of both free and total acidity

Meyer, Ivy and McEnery (1924) showed on Pavlov pouch dogs that bile stimulates gastric secretion They found that cholecystectomy does not cause a depression of gastric secretion and they thought that through its role on fat bile may have an indirect excitatory action on the gastric secretory mechanism

Still and Carlson (1929) produced an immediate but temporary inhibition and great diminution of gastric secretory response to a test meal by intravenous injection of bile These experiments were not confirmed by Kosaka and Lim (1933) who used toxic doses of bile by intravenous injection.

Kim and Ivy (1936) found little secretagogue action produced by hepatic bile in contact with the gastric mucosa for periods of 30 minutes which corresponds to ' normal since regurgitated fluid would be evacuated from the stomach in half an hour (Regurgitated bile is gall bladder bile which is 10–20 times more concentrated than hepatic bile)

Kaulbersz and Winfield (1942) observed that when 2 g of bile were placed into fasting dogs stomachs 5–35 minutes before histamine injection diminution of both secretion and acidity was noted in the Heidenhain pouches in 50 per cent of the experiments When bile was given after histamine injection no inhibitory effect on secretion occurred nor was there any increase in the amount or acidity of the secretion in the pouch Bile introduced into dogs stomachs with Pavlov pouches induced an increased amount of gastric secretion from the pouches after histamine injection In dogs with gastric fistulae the amount and acidity of gastric secretion was found to be exceedingly high in several instances following histamine injection and introduction of bile These high readings were never equalled by the [illegible] effect alone In certain instances histamine and bile produced [illegible] small amounts of secretion They thought therefore, tha the [illegible] gastric secretion was partially stimulatory and partially [illegible]

did not influence the inhibition but nullified the stimulation of secretion The inhibitory effect was predominant in Heidenhain pouches and the stimulatory effect in Pavlov pouches In dogs with gastric fistulae the combined inhibitory and stimulatory effects produced a variety of results which seemed to justify the supposition that bile introduced into the stomach initiates a nervous stimulation producing an increase of gastric secretory activity, and that when the bile progresses into the intestine absorption produces a decrease of gastric secretory activity

Beamer, Friedman, Thomas and Rehfuss (1944) found in dogs, with gastric and duodenal fistulae, that following the introduction into the intestine of dogs, without special precautions substances such as ground meats or meat digests, a secretion of gastric juice was normally obtained When bile was prevented from entering the stomach or accumulating in the intestine and only isotonic solutions were used, little or no gastric secretion was evoked In Pavlov pouch dogs in which products of protein digestion were instilled into the intestine, while bile was allowed and the test solution prevented to regurgitate, secretion of gastric juice was observed to commence within half an hour after the first appearance of bile in the stomach The volume of gastric secretion varied roughly in proportion to the volume of bile which regurgitated and the duration of contact of the bile with the gastric mucosa When solutions of dog or ox bile were placed in the main stomach of the Pavlov pouch dog, the secretion of the pouch amounted on the average to 6 2 cc during the first hour following bile administration while the volume for the control hour preceding bile administration was only 0 7 cc thus confirming the early work of Sokolov (1904) Contrary to the results of Meyer, Ivy and McEnery (1924) they found that bile alone in the intestine did not stimulate gastric secretion The instillation of bile into the stomach resulted in vomiting and a brief augmentation of the rate of gastric secretion

Kaulbersz and Bilski (1949) observed in dogs that bile introduced through a gastric tube evoked an increase of volume of secretion from Heidenhain pouches affecting only slightly the acidity and the peptic power They suggested that in cases of hypersecretion the regurgitation of bile into the stomach may present a source of continuous stimulation

The effect of bile on intestinal motility

While the presence of bile in the stomach produces an increased motility it has the opposite effect on the small intestine

Fubini and Luzzati (1888) timed the passage of a pea through a loop of intestine, it was found to pass through the lumen more rapidly after bile had been injected into the lumen than before Eckhard (1899) injected 1 cc of bile into the duodenum of a rabbit and it remained quiet for 10 minutes Injection of bile into the intestine resulted in wave like movements along the intestine Hallion and Nepper (1907) found that bile in contact with the intestinal mucosa has a local stimulating influence on the small intestine especially upon the duodenum Schupbach (1908) observed that bile has an

inhibiting effect on the movements of the small intestine and an accelerating effect on those of the colon A weakening of activity and a decrease of the number of contractions of the small intestine by the strip method of Magnus was observed by d Errico (1910)

Ott and Scott (1909) observed increased peristalsis in a Vella fistula by the oral administration of 2 g of bile but they agreed with Schupbach (1908) that direct application of bile inhibits the surviving excised small intestine of cat or rabbit while it stimulates the large intestine

Boulet (1921) who studied two human subjects 15–20 minutes after decapitation observed that bile had an inhibitory effect on the motility of the ileum and the colon This confirmed his previous observations on animals

Nakata (1933) confirmed the observations that when the serous coat of an intestinal strip was exposed to the action of bile it had a depressing effect on the motility but when the mucosal coat was exposed even to a much stronger concentration of bile the effect was slight or absent

Horrall (1938) stated that he and his collaborators observed that ox bile injected into the duodenum produced a curve of increased activity very similar to that of sodium glycocholate and dog gall bladder bile A period of relaxation frequently preceded the stimulation produced by the injection of those substances

In a series of experiments on caecostomized dogs in which the proximal and distal activity could be correlated by two tandem balloon systems Galapeaux Templeton and Borkon (1938) observed that the injection of 10–20 cc of gall bladder bile in contradistinction to tap water was followed by a marked depression in colon activity lasting from 50 to 100 minutes Defaecation followed a few minutes after injection and marked tenesmus was usually manifested Haney Roley and Cole (1939) found that the introduction of gall bladder bile from the dog into the proximal end of a loop of intestine is promptly followed by a marked increase in the rate of propulsion A solution of bile salts is fully as effective as bile They observed in Thiry-Vella loops in the dog that the local application of bile stimulates the motor activity of the small intestine that this effect is due entirely to the presence of bile salts and that the action of bile salts on the glands of the jejunal mucosa best explains this result They suggested therefore that bile salts may play an important role in the normal regulation of the propulsive movement of the small intestine Ackerman Curl and Crandall (1941) observed that after a fatty meal the rate of gastric emptying in the bile fistula preparation is slower than in normal dogs but the administration of bile salts with a fatty meal brings the gastric emptying time of the bile fistula dog to within normal limits

It may be stated in conclusion that the evidence tends to show that bile has a stimulating effect on the stomach the upper part of the small intestine and the colon but does not markedly affect the motility of the small intestine

The effect of bile on the gastric mucosa

(The reader is referred to chapter 8 p 152 which deals qith the effect produced experimentally by bile on the gastric mucous membrane)

Bile is not found ordinarily in the stomach although small quantities of a dilute solution may appear towards the end of a meal

An excess of bile in the stomach causes vomiting as was observed by Bouisson (1843) when he gave 120 cc of bile to a dog by mouth Claude Bernard (1856) thought that bile precipitated the pepsin when it reached the duodenum Corvisart (1857) believed that it was precipitated by the acid of the chyme Harley (1860) supported this view Naunyn (1868) observed loss of appetite in a dog which was given 2 g of sodium choleinicum in sausage

The toxic effect of bile on the gastric mucous membrane was shown by Rywosch (1891) to be dependent on the bile salts and their derivatives He demonstrated that bile acts as a protoplasmic poison on red and white blood corpuscles as well as on ciliated and liver cells Similar observations were made by Neufeld and Handel (1908)

In reviewing the causes of chronic glandular gastritis Ewald (1893) refers to the well known experiments of Dastre (1890) and Oddi (1888) who found that large quantities of bile in the stomach had no influence on the digestion, an observation which contradicted previous authors as well as those of van der Velden, Malbran Riegel, Weill and his own which without doubt showed that regurgitation of bile was the cause of gastric disturbances

Smith (1914) found that when he transplanted epithelial tissue into the gall bladder, necrosis only occurred in that part of the graft which was in direct contact with bile, while the remaining part, which was protected through the infolding of the mucous membrane, escaped damage for a considerable time Tashiro (1917) suspected that a number of agents known to produce ulceration of the gastric mucosa in guinea pigs such as adrenaline thyroxine and bacterial toxins reduce the phosphatide contents of the blood and thus remove this protective effect against the bile salts Alcoholic extracts of bile were fed to 18 rats by Cooper (1923) Most of the rats died within 48 hours all being dead by the seventh day At necropsy, the intestine and stomach were haemorrhagic and there were erosions of the gastric mucosa in 3 rats Hosono (1931) reported that gastric haemorrhage follows the feeding of sodium taurocholate and sodium glycocholate

Leriche (1931) drew attention to the important fact that hydrochloric acid liberates the bile salts from bile

Tamesue (1934) observed that autolysis of the gastric mucosa occurs at *p*H 4 0–8 0 and that hydrogen inhibits and nitrogen stimulates the effect Bile acids inhibit the effect depending on their concentration, 1/1,000 concentration has no effect He emphasized that the cytolysis of the gastric mucosa in the presence of HCl is considerably increased and that it is essential for its action He measured the permeability of the gastric mucosa (in pigs) of bile salts and acid and found that very weak solutions of bile salts show a marked effect Concentrations of 1/5 000 –1/10 000 of sodium taurocholate are effective

According to Sobotka (1937) bile and bile acids precipitate the pepsin in the acid gastric juice thereby inactivating it an effect which is not reversed by re acidification (Burkart, 1868) and thus is not merely due to an unfavour

able pH, but mainly to the precipitation of the bile acids by the gastric acid and simultaneous absorption of the pepsin on the precipitate

Maier and Grossman (1937) observed considerable digestive disturbances as a result of complete duodenal regurgitation

Wangensteen Varco Hay Walpole and Trach (1940) considered the Schmilinski operation which involves the regurgitation of bile into the stomach as a highly undesirable operation an opinion held by Ivy Grossman and Bachrach (1950) and many others

Fidler Innes and Davidson (1941) have drawn attention to the fact that digestion of cellular elements in bile takes place rapidly on standing

Driver Dozier and Denham (1943) showed that substances which increase the permeability of the intestinal mucosa by a lowering of surface tension or other means facilitate the formation of ulcer According to Lambling and Gosset (1947) biliary reflux produces an erythematous oedematous gastritis

Grant Grossman and Ivy (1948) examined the effect of bile on the gastric mucus Mucus collected after exposure of the gastric mucosa to 1 per cent acetic acid was opaque white and extremely viscous with a pH of 7–8 5 which falls to 2–3 at the end of the secretion period Microscopically they observed intact gastric surface cells suspended in the alkaline the nuclei alone in the acid state At the optimum pH of 7–8 8 bile forms with the mucus a transparent homogeneous mixture When mixed with saline clear acid gastric juice 0 2 NaH_2PO_4 more duodenal pouch juice the mucus remained in a separate phase The cellular elements disappeared from the mixture Opacity and high viscosity of the original mucus was due apparently to the cellular elements suspended in it They found disintegrative changes in the gastric surface cells in mucosa exposed to bile for a few mintues They concluded that cytolyis of these cells by bile suggests potential danger to the mucosa should suitable conditions for the action exist

Lambling and Gosset (1948) describe a dyspeptic syndrome conditioned by reflux of bile which they consider to be a pathological phenomenon Duodenal dystonia and vascular spasm produce ischaemia followed by gangrene and a superimposed neurovegetative disarrangement

Bernard (1950) corroborated these conclusions on the proteolytic action of bile on the gastric mucosa He found experimentally that bile produces ulcerations of the gastric mucous membrane In a rat subjected to stress in order to provoke an ulcer he found that the stomach was filled with green bile Both macroscopically and microscopically the mucosa appeared normal but for a limited focus in a fold of mucosa to which bile was adherent Contact with bile immediately altered the mucosa which acquired a marked eosinophil coloration The superficial cells became retracted the deeper cells being swollen and filled with eosinophil granulations These lesions showed a distinct progression from the surface to the deeper layers which where produced by contact with bile

According to Wangensteen (1951) the Schmilinsky procedure is definitely ulcerogenic Complete intragastric regurgitation of bile and pancreatic juice stimulates the gastric phase of gastric secretion interminably

THE TOXICITY OF BILE

The toxic effect of bile on the nervous system was recognized since the time of Hippocrates The effect on the brain and nerves, the heart and blood pressure and on skeletal muscle has been reviewed comprehensively by Horrall (1938)

Horrall (1938), after referring to many contradictory observations by the earlier authors, concluded that the variations of the toxicity of different biles may be explained in various ways (1) the quantity of bile acids in the bile may vary considerably, (2) the kind of bile acids in the bile may vary (taurocholic acid in dog bile and glycocholic acid in ox bile), (3) the amount of protective substances (cholesterol, protein) may vary substantially, and (4) specific proteins or other constituents may cause reactions

Magendie (quoted by *Horrall, 1938)* reported in *1824* that *1* g of bile injected into the crural vein of dogs killed the animal in a few moments, whereas when injected slowly into the portal vein, it caused no disturbance Bouisson *(1843)* injected *human gall bladder bile* into the jugular vein of rabbits, killing all animals Filtered bile had only a mild effect

The depressing and exciting elements contained in the bile are mutual antagonists, the total effect being an algebraic sum (Meltzer and *Salant*, 1906) Whole bile is more toxic than either of its major constituents (Greene and Snell, 1928) Horrall and Carlson (1928) have shown that bilirubin has no effect on the heart, urobilin appears to be purely an excretion product Still (1929) found that bilirubin is a non toxic substance, that bile acids are the most toxic substances found in bile, that the order of toxicity of the bile acids is (1) choleic, (2) desoxycholic, (3) glycocholic, and (4) cholic, and that the toxicity of bile lies in the cholate radical

Horrall and Carlson (1928) recorded the manifestations of toxicity produced by bile as heart rate decreased and irregular, *blood pressure decreased*, vomiting, bloody diarrhoea, anuria or, if there is urine, it contains albumin, haemoglobin, red blood cells, and later, casts, cellular, then hyaline, *the respiration amplitude is decreased, the rate increased oedema of the* lungs, and frequently pneumonia, in the central nervous system, convulsions (tonic, clonic or intermittent) and, later, coma and death

The toxicity of bile varies, according to Horrall (1931), directly with its salt content and specific gravity and, therefore, the gall bladder bile has a greater toxicity than hepatic duct bile or fistula bile He quotes Stadelmann *(1896) who considered sodium taurocholate 10* times more toxic than sodium glycocholate

According to Strain and Marsch (1936) bile salts act as toxic substances by inhibiting the oxygen consumption of the tissues

It may be noted with particular interest that Tsuruta (1931) concluded from his experiments as follows The male is more susceptible to the toxic action of bile salt than the female This is true, not only for the frog's muscle, but also for the stomach mucosa of guinea pigs Whether this difference is due to the different nature of the tissue protein or to the phospholipid content

we are not prepared to answer And it is equally difficult to answer a question as to whether this difference in susceptibility of the tissue to bile salts is responsible for the greater incidence of gastric ulcer in males than females in the case of the human

The effect of bile on the blood

This is of particular interest as it affects the problem of gastric haemorrhage

Rywosch (1891) found that coagulation of blood was prevented by 0 4 per cent taurocholate Doyon and Gautier (1909) observed that 1 ml of bile prevents the coagulation of 10 ml but not of 15 ml of plasma and that 1 ml per kilogram of body weight of bile or of a 10 per cent taurocholate solution when injected into the mesenteric vein suppresses the coagulability of the blood for a few hours

Neufeld and Handel (1908) stated that bile salts are a protoplasmic poison and have a cytotoxic effect causing haemolysis of red cells disintegration of white cells disruption of spermatozoa haemorrhage albuminuria and lysis of protozoa

Tatum (1916) and Bradley and Taylor (1917) showed that bile or its salts has a very marked cytolytic effect on the cells of various organs and that this disintegrating effect is quite distinct from autolysis They also showed that this is not due to the activation of enzymes by bile or to a co-ferment in bile but represents a straight destructive effect presumably of a chemical nature

Horrall (1931) observed that bile mucin, which is different from mucin secreted elsewhere reduces the toxicity of bile Williams (1932) has shown that human serum diminishes the toxicity of bile salts Haemolysis is produced by 0 625 per cent bile salt in sodium chloride solution but requires 2 5 per cent when used with human serum

Effect of bile on micro-organisms

The action of bile and of bile acids on microbes especially on pathogenic invaders, is manifold and *in vitro* experiments do not always allow one to predict what will actually take place *in vivo*

Bacteria were present in bile in the gall bladder in 58 per cent of 735 cases operated on at the Johns Hopkins Hospital The post operative diagnosis was gallstones in 599 cases and cholecystitis in 136 cases *Bacillus coli* was present in 49 per cent of these cases and *B typhosus* in 19 per cent (Blalock 1924)

Yeasts are resistant to bile

Bile peritonitis

According to Wangensteen (1926) leakage of sterile bile into the peritoneal cavity is not innocuous as was suggested by some authors The experimental animal dies within a short time of cholaemia due to the toxic action of the bile salts when a well functioning biliary fistula from which bile escapes into the peritoneal cavity is established

According to Horrall (1938) bile peritonitis is caused by the toxic action of

bile acids Bile acids exert a toxic effect on the heart, kidneys, blood and blood capillaries and on all tissue with which they come in contact Bacteria have little or no effect if the peritonitis is fatal within a few hours Secondary surgical shock is a very important result of the toxic action of bile acids It has been well established that bile, injected subcutaneously, causes tissue necrosis, and even a large aseptic abscess

The effect of bile on the gall bladder

Why does bile not cause necrosis of the gall bladder? This question is as pertinent as the question why hydrochloric acid does not cause necrosis of the gastric mucosa or trypsin destroys the pancreas Horrall (1938) explains that bile is very toxic to all the body tissues, especially when the salts are concentrated The bile in the gall bladder is from 5 to 20 times more concentrated than that in the hepatic duct The liver bile is alkaline as shown by vital staining (Rous, 1925), the *p*H being greater than 7 4 and less than 8 4 As the bile passes into the gall bladder and is concentrated, the alkalinity diminishes, causing the *p*H to return to a neutral or slightly acid state In the centre of the bile in the gall-bladder the *p*H is 6 4, but about the periphery it is lower at 5 4 The wall of the gall bladder is also slightly acid in spite of the fact that it consists largely of connective tissue The protective substances which occur in the bile are cholesterol, lecithin fats and proteins These substances actually diminish the cytolytic activity of the bile salts Mucin is added by the lining of the bile ducts and gall bladder This acts in two ways, first, as a mechanical protective covering for the mucosa, and second as a chemical neutralizer of the bile salts Both the true and pseudo mucins are very soluble in alkalis such as bile salts It appears that the acidity of the living liver cells and gall bladder mucosa protect themselves against strongly necrotic alkaline bile by throwing out enough acid to make a zone of neutrality between liver cells and the bile

Womach and Bricker (1940) produced cholecystitis by the injection of concentrated bile into the gall bladder but it should be noted that the damage occurred only after ligation of the cystic duct—thus introducing an additional factor in the experiment According to Berman, Snapp Ivy and Atkinson (1940) there is no evidence that bile acids are toxic to the liver

Gatsch, Battersby and Wakin (1946) believed that cholecystitis is produced by pancreatic juice and bile salts When they injected bile salts into the portal venous system, they observed no change in the liver though there was intense inflammation of the gall bladder

The effect of bile on the pancreas

Although the human duct of Wirsung joins the common bile duct (in many species these ducts remain independent and enter the duodenum separately) nevertheless, if bile enters the pancreatic duct it gives rise to extremely serious consequences

Acute pancreatitis and haemorrhagic necrosis have been produced experimentally by allowing bile to enter the pancreas (Claude Bernard

1856 Opie 1901, 1910 Flexner, 1906, Archibald and Mullally 1913, Whipple and Cook 1918, Archibald, 1918, Brock and Morrel, 1919 Wangensteen, Leven and Manson 1931, Wolfer, 1931 Bottin 1932, Jones, 1932 Elman 1942)

A large number of irritating substances when injected into the pancreatic duct are capable of causing in animals, the same lesions that are observed in the human —gastric juice, (Hlava, 1890), formalin, sweet oil, fatty acids and sodium soaps of the fatty acids (Opie, 1901), duodenal contents (Polya 1906), weak solutions of hydrochloric nitric and chromic acids and alkalis Flexner 1906) Bland substances have been found to do little or no harm (blood blood serum, agar agar, gelatine paraffin starch emulsion and also cultures of certain bacteria when not too virulent or in too great quantity)

According to Archibald (1919) the essential pathological lesion in pan creatitis is necrosis of the pancreatic cells or masses of cells This is the primary effect (Opie and Meakins 1909) Haemorrhage inflammation, infection are all secondary effects

According to Mann and Giordano (1923) an anatomical and physiological basis for the theory that reflux of bile may occur in the pancreatic duct does exists In only 3 5 per cent of 200 human specimens was it possible to obstruct the exit of the ampulla and cause bile to pass into the pancreatic duct Wolfer (1931) found that in all cases in which pancreatic juice was introduced into the gall bladder of the dog there followed unmistakable pathological changes in the wall of the gall bladder Bisgard and Baker (1940) showed experimentally that reflux of pancreatic juice into the gall bladder in the presence of biliary stasis invariably produced permanent pathological changes in the gall bladder (acute aseptic cholecystitis with necrosis of the wall of the gall bladder)

It is significant that the secretion pressure in the pancreatic duct is greater than in the bile duct (Dragstedt Haymond and Ellis 1934)

The relation of bile to carcinoma

Ivy (1944–45) suggested that the action of bile salts upon fat soluble substances would influence the action of carcinogenic hydrocarbons in the stom ach Thus methylcholanthrene which has a close chemical relationship to the normal constituents of the bile dissolved in bile might produce a lesion where methylcholanthrene alone failed to do so

Barrett (1946–47) pointed out that the areas of the intestine which are normally most exposed to bile are the site of far less cancer than in the stomach, which is normally only mildly exposed

Cholecystogastrostomy

Oddi (1888) is reputed to have been the first to perform cholecystogastros tomy His object was to find out the effect of bile on gastric acidity In his day bile was held to have a pernicious effect on digestion by neutralizing the acid and by precipitating pepsin and albumin (Hammersten Fredericq Landois Brücke Bernard Foster)

Mocquot (1911) and Grey (1916) found that this operation had no appreciable effect on the gastric acidity in dogs Their observations were confirmed by Robinson (1930) Babcock (1920) believed that the operation favoured the neutralization of acid and he recommended it for the treatment of gastric ulcer

Gatewood and Poppens (1922) who anastomosed the gall bladder to the stomach, duodenum and colon in dogs, observed that the gall bladder invariably becomes infected regardless of the viscus used for anastomosis Lehman (1924) found that no variation of the mechanical plan of the operation prevented the hepatitis Du Bose (1924) referred to cholecystogastrostomy and cholecystoduodenostomy as operations of necessity rather than of choice Marinelli (1925) found that there was irritation and inflammation in every instance wherever the gall bladder was sutured to the digestive tract

Braithwaite (1926) recommended cholecystogastrostomy as the operation of choice for inaccessible gastric ulcer Wangensteen (1928) reported cholangitis following cholecystogastrostomy for a malignant lesion of the head of the pancreas Beaver (1929) found invariably that infections of the biliary tract and liver followed cholecystogastrostomy Robinson (1930) who advocated cholecystogastrostomy for gall bladder disease considered it '*unlikely that this operation can have any beneficial effect in the treatment* of gastric ulcer, as has been claimed' Gatewood and Lawton (1930) found that from an experimental standpoint, infection of the gall bladder invariably follows cholecystogastrostomy regardless of obstruction of the common bile duct Hepatitis and cholangitis are the rule Similar observations were made by Gage (1930–31), Eliason and Johnson (1936), Sandblom, Bergh and Ivy (1936), Graham (1938), Walters (1939), Bengolea and Velasco-Suarez (1939), Glass (1940), Allen (1940), Soupault (1940), Mallet Guy (1940), Zollinger (1940), Brackin and David (1941), and Gordon Taylor (1942)

Whipple (1938) stated that "the rare successes, not the many failures, appear in the literature'

Braithwaite (1943–44) who admitted having been obsessed by the value of bile in the stomach found that the late results of the operation which he had advocated as the treatment of choice for inaccessible gastric ulcer (Braithwaite, 1926) *were unsatisfactory and the operation was abandoned*

Cholecystectomy

Extirpation of the gall bladder causes as a rule dilatation of the *ductus choledochus* which develops into a vicarious reservoir If, however, the function of the sphincter is impaired by pathological causes or experimentally, then no dilatation occurs and a continuous flow of bile into the intestine is established (Rost, 1913, Mann, 1917, Judd and Mann 1917)

Meyer Ivy and McEnery (1924) found that cholecystectomy does not cause a depression of gastric secretion

CHAPTER 17

AUTHOR'S THEORY OF CHRONIC ULCER FORMATION

It may now be suggested that the elements required for the construction of a theory of the causation of chronic peptic ulcer must be based on physio pathological considerations

Expressed in its simplest form, it may be postulated that the tissues react to stimuli in the following manner

(*a*) A threshold stimulus gives a normal physiological response

(*b*) A repeated stimulus gives an exaggerated physiological response (hyperfunction—a true *réflexe de défense*),

(*c*) A sustained stimulus gives a pathological response (increased irritability a reduced local resistance and ultimately breakdown of the tissues)

Summation of the responses to stimuli (by the introduction of the time factor) converts a physiological into a pathological process

The stages in the development of the lesion are parallel manifestations to the responses of the conditioning stimuli These appear in the following order (1) the Syndrome of Hyperfunction (2) the inflammatory reaction and (3) the necrosis of the tissues

The method of approach to the solution of the problem of chronic peptic ulcer may be divided into three parts

The first concerns the identification of the nature of the stimulus It may be either of a physical or of a chemical nature That it is not wholly physical in nature is shown by the fact that mechanical trauma cannot produce the lesion That it can be of a chemical nature is supported by much evidence which shows that chemical agents have a markedly destructive effect on the gastro-intestinal mucous membrane

The second concerns the site of the injury produced by the stimulus Since the chronic lesion starts on the surface of the mucous membrane before it penetrates into the deeper structures of the wall of the organ it must be produced by direct contact of the toxic agent with the mucous membrane

The third concerns the mechanism which is reponsible for the persistence of the stimulus The prolonged presence of fat in the stomach after an initial inhibition produces a hypersecretion of gastric juices (hyperchlor hydria) and causes the regurgitation of intestinal juices and bile into the stomach Bile which normally performs its function in an alkaline medium acts as a powerful irritant on all tissues in the extra biliary channels

particularly so in an acid medium It reduces the surface tension of the gastric mucous membrane and, therefore, accelerates its destructive effect on the tissues which respond by a generalized inflammatory reaction of the mucosa (superficial hypertrophic gastritis—the pre-ulcerative stage)

The continued action of the irritant on the inflamed mucous membrane reduces local resistance and, finally, causes the breakdown of the tissues

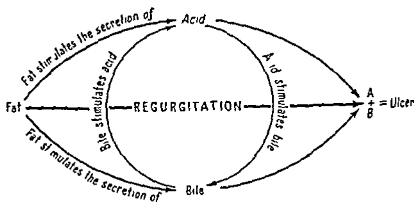
Since hypersecretion of acid stimulates the secretion of bile and bile stimulates the secretion of acid, a vicious circle is formed

It may, therefore, be deduced that bile is the original stimulus which initiates the lesion, prevents its healing and maintains its chronicity

The mechanism which is responsible for ulcer formation may be represented by a simple equation $A + B = U$, in which A = acid, B = bile and U = ulcer The elimination of A or B abolishes the equation It follows, therefore, that if either the acid factor or the bile factor is removed, the morbid process is arrested and the ulcer heals

It will be noted that the elements which are responsible for the initiation of the lesion are also responsible for its maintenance and chronicity, but since the chronic gastritis appears before the appearance of the ulcer it may be said that chronic ulcer is "chronic' before it is 'ulcer"

The practical application of this theory will be developed in the section which deals with the Clinical Considerations



Author s representation of vicious circle involved in chronic ulcer formation

CHAPTER 18

THE ROLE OF FAT IN THE ECONOMY OF THE ORGANISM

PHYSIO CHEMICAL CONSIDERATIONS

THE COMPOSITION OF FAT

The fatty substances concerned in this Study may be divided into three main groups

(1) Neutral fats, which are fatty acid esters of the trihydroxy alcohol glycerol The fatty acids occurring in the neutral fats of the body are (*a*) saturated acids of the general formula $C_n H_{2n} O_2$ the main representative of which are palmitic acid ($C_{16} H_{32} O_2$) and stearic acid ($C_{18} H_{36} O_2$), and (*b*) unsaturated acids, of the general formula $C_n H_{2n-2} O_2$ which contain one or more pairs of carbon atoms united by a double bond (C C) at some point of the carbon chain—of which oleic acid ($C_{18} H_{34} O_2$), with one double bond between the ninth and tenth carbon atoms occurs in large quantities

(2) Waxes which are esters of fatty acids and alcohols other than glycerol Of these esters of mono-hydroxy alcohol, cholesterol ($C_{27} H_{46} O$) occurs in animal fat

(3) Compound lipids which are fatty acid esters containing in addition an alcohol and fatty acids Of these the phospholipid lecithine, a glyceride of fatty acids, combined with choline and phosphoric acid, is the most important

Compound lipids usually contain in addition to palmitic stearic or oleic acid more highly unsaturated fatty acids such as linoleic acid ($C_{18} H_{32} O_2$ with two double bonds) linolenic acid ($C_{18} H_{30} O_2$ with three double bonds) and arachidonic acid ($C_{20} H_{32} O_2$ with four double bonds)

Esters of the triatomic alcohol glycerol are by definition fats when they are solid at ordinary temperatures and oils when they are liquid

The *physical* properties of fat concern the specific gravity, the melting point the solidification and titre the refractive index and the rotary power

The *chemical* properties of fats are characterised by the following

(1) *The acid value* which is determined by titration of the free fatty acid with caustic soda It is a measure of the degree of hydrolysis of the fat.

(2) The *saponification value* which determines the amount of caustic potash which is neutralised during saponification

(3) The *iodine value* which is the amount of halogen calculated as iodine which is taken up by the unsaturated acid

(4) The *Hehner value* which gives the percentage of fatty acids insoluble in water that are yielded on saponification by a fat

(5) The *Reichert Meissl value*, which is a measure of the amount of lower fatty acids entering into the composition of a fat which volatilises in a current of steam

(6) The *acetyl value*, which gives the number of milligrams of caustic potash required to neutralise the acetic acid liberated on saponification of 1 g of acetylated fat

CHOLESTEROL

Although cholesterol is not chemically related to fats, there is an intimate physiological relationship between these substances

Cholesterol is a sterol, comparatively inert, solid, insoluble in water, but soluble in alcohol, ether and chloroform Its chief sources in the food are yolk of eggs, liver, kidney, brain and fats (cream, butter and meat fat) It is an essential constituent of all cells and fluids in the body and exists either in the free state or combined with fatty acids to form cholesterol esters In bile, it occurs only in the free state and tends to vary with the amount in the blood, where it exists in a free state in the red blood corpuscles while in the plasma more than half is present as ester The normal level is 0 15–0 2 per cent Large amounts are present in the adrenal cortex, the ovaries and the nervous system particularly the brain

Most of the cholesterol derived from cellular disintegration is retained in the body Cholesterol when given orally, is absorbed only in small amounts unless some fatty material is also present in the intestine The ingestion of food rich in cholesterol over a period of time raises the blood cholesterol

Bile and pancreatic juice aid its absorption Combination with the bile acids increases its solubility and the esters are hydrolysed by pancreatic and intestinal enzymes The esters are resynthesized before reaching the lymph stream, which is the main route by which the cholesterol is absorbed Synthesis is proved by the fact that the output may considerably exceed the intake over long periods of time, the blood contains an enzyme which will split the esters and cause synthesis (Sperry and Schoenheimer, 1935) Part of the absorbed free cholesterol is excreted in the bile and part is changed into coprosterol by hydrogenation and eliminated in the faeces Some of the biliary cholesterol is reabsorbed in the small intestine The cholesterol plus coprosterol in the faeces is usually greater than the cholesterol content in the diet Cholesterol can be found in normal urine (Gardner and Gainsborough 1925) Blood cholesterol is low during acute infections but returns to normal with recovery, it is low with chronic anaemia but high with thyroid deficiency, diabetes mellitus nephrosis, and also during pregnancy The increased cholesterol of the blood during fat absorption is mainly due to the absorption from the pancreatic and intestinal juices and the bile It has been suggested that cholesterol is one of the constituents of bile which make it so efficient in the emulsification of fats and therefore, in their digestion and absorption

Bridges (1941) considered that cholesterol is a lipid of paramount importance It is a vital constituent of nerve tissue cells, and is responsible in part

for the semi solid constituency of living cells despite their large water content (75 to 85 per cent) Increase in cholesterol concentration enables cells to hold greater quantities of water pathologically visible oedema Continuous feeding of diets high or low in fat raises or lowers the blood cholesterol level which is normally 0 18 per cent. The infant receives very little cholesterol from milk Cholesterol or its derivatives located in the skin are transformed into active Vitamin D by solar irradiation

LIVER AND FAT METABOLISM *

Brief reference will be made to the development of fatty livers in respect of fat metabolism because it is intimately related to cirrhosis of the liver

Allan Bowie McLeod and Robinson (1924) observed that totally pancreatectomized dogs which were maintained on an adequate supply of insulin developed fatty livers which could be prevented by the administration of raw pancreas Following the suggestion of Leathes and Raper (1925) that phospholipids were involved in fat transport from the liver, Hershey (1930) found that lecithine successfully replaced the administration of raw pancreas Hershey and Soskin (1931) found that egg yolk lecithine prevented the death of the animals

The development of fatty livers in rats on a high fat diet is prevented by lecithine (Best, Hershey and Huntsman 1932) This effect is produced by the choline fraction of lecithine (Best and Huntsman 1932, Best Ferguson and Hershey 1933) Toxic states and starvation induce a fatty infiltration of the liver which is dependent on the quantity of fat available for mobilisation (Dible, 1932 Dible and Libman 1934 Best and Campbell 1938) Welch (1936) found that choline promotes the formation of phospholipids and consequent removal of neutral fats from the liver

Feeding rats on a high liver diet produces fatty livers (Beeston and Wilkinson 1936)

Some authors (Aylward and Holt 1927, Ralli Rubin and Present 1938 Best and Ridout 1938 Julian Clark Vermeulen Donovan and Dragstedt, 1942–43) believed that no lipotropic factor other than choline existed in the pancreas while others (Channon Loach and Tristram 1938) believed that a specific factor other than choline existed in the pancreas

Channon and Smith (1936) synthesized the ethyl homologue of choline which showed strong lypotropic activity

Best and Campbell (1936) found that the ketogenic extract of anterior pituitary gland produced an intense infiltration of fat and a rapid increase in the size of livers of fasting rats Adrenalectomy abolishes the ketosis and prevents the accumulation of fat in the liver (McKay and Barnes 1937) Dragstedt Prohaska and Harms (1936) found that an alcoholic extract of pancreas (lipocaic) prevented the fatty degeneration of the liver Choline

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* Substances wh ch prevent or remove accumulation of fat in the li er are termed lipotropes

or lipocaic have no influence on ketosis according to Mackay and Barnes (1938b), but Julian, Clark, Prohaska, Vermeulen and Dragstedt (1942-43) found that it was decreased by lipocaic

Tucker and Eckstein (1937) discovered the lipotropic property of methionine, and Channon, Manifold and Platt (1938) suggested that it was the effective amino acid This was confirmed by Griffiths and Wade (1939)

Channon, Loach, Loizides, Manifold and Soliman (1938) suggested that all proteins have a lipotropic action which is due to their amino acid contents

Perlman and Chaikoff (1939) found that choline stimulates the synthesis and transfer of phospholipids

Betaine, which is a precursor of choline, has a lipotropic effect (Platt, 1939, du Vigneaud, Chandler, Moyer and Keppel, 1939)

Connor and Chaikoff (1938) in dogs produced fatty livers with alcohol which were shown to be due to choline deficiency (Best, Hartroft, Lucas and Ridout, 1949) and which could be prevented by the administration of adequate amounts of choline

Chaikoff and Connor (1940) observed that the continued presence of an excessively high amount of fat in the liver stimulates hepatic fibrosis even in normal dogs and may cause the death of the animals

According to Frazer (1940) there is little evidence that choline stimulates fat oxidation or that it is concerned with phospholipid formation in the livers as a factor of intermediate metabolism

Welch and Landau (1942) have shown that arsenocholine (an analogue of choline containing arsenic in place of nitrogen) is lipotropic and also enters the lecithine molecule The observation that the triethyl homologue of choline is incorporated into the phospholipids suggested, according to McArthur, Lucas and Best (1947) that the intact molecule of choline rather than its labile methyl group is responsible for its lipotropic action

Entenman, Chaikoff and Montgomery (1944) found that the active fraction of the anti fat substance is not dyalizable, that it is soluble in dilute acid and that the choline free fraction derived from the raw pancreas prevents fatty livers Since depancreatized dogs suffer from a reduction of plasma choline, Chaikoff, Entenman and Montgomery (1947) concluded that depletion of choline storage accounts for the development of fatty livers, and since free methionine also prevents fatty livers, the synthesis of choline from methionine is not impaired in the completely depancreatized dog

There is a direct relationship between high fat diets and the requirements of choline and labile methyl groups (Elvehejm and Krehl, 1947)

Edible fats as obtained commercially are almost free from choline

Vitamin B_{12} and folic acid appear to have a lipotropic effect, the former in the biosynthesis of labile methyl groups, the latter in transmethylation* of the choline molecule

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* "Transmethylation is the transfer of labile methyl groups from choline and betaine to homocysteine to yield methionine the possession of a labile methyl group is a characteristic common to choline and methionine (du Vigneaud 1952)

CHOLESTEROL IN RELATION TO THE FATTY LIVER

When rats are fed on diets containing cholesterol they develop fatty livers which are characterized by the presence in the liver of excessive amounts of cholesteryl esters while at the same time considerable deposition of glyceride may occur This variable increase of the glyceride content of the cholesterol fatty liver (antilipotropic effect) has been shown to depend on a number of factors Cholesterol is not significantly absorbed unless fat is present in the diet as shown by Thannhauser (1923) in man Sano (1924) in dogs and Cook (1938) in rats Cholesterol is deposited throughout the body, except the brain (Page and Menschick 1932) There is a marked rise in cholesterol, both free and combined in the thoracic duct lymph during fat absorption (Spiers and Himwich, 1934) Diets containing cholesterol cause a change in the nature or an increase in the amounts of liver lipids (Best, Channon and Ridout 1934)

Loizides (1938) suggested that the progressive increase in the liver cholesterol with increasing fat in the diet must be regarded as a result of increased cholesterol absorption Cholesterol is absorbed irrespective of the type of fat fed (Cook 1938) Cholesterol metabolism is bound up with an increase of fatty acids in the faeces the amount of cholesterol missing is approximately equal in amount to the acids recovered Rats synthesize more cholesterol on a high fat diet than on a low fat diet, the increase of cholesterol being greater with an unsaturated fat than with a saturated fat (Eckstein 1938)

Perlman and Chaikoff (1939a, b) found that cholesterol decreased and choline stimulated the phospholipid turnover in the liver of cholesterol fed rats

There appears to be a physiochemical antagonism between cholesterol and lecithine

FAT SYNTHESIS

The conversion of carbohydrates into fat appears to pass through the following stages (*a*) glucose is reduced to lactic or pyruvic acid to form acetaldehyde condensation of acetaldehyde molecules with or without pyru vic acid yielding a long chain of unsaturated aldehydes or keto-acids which in turn are oxidized to fatty acids, (*b*) the conversion of glucose into glycerol is generally thought to occur in such a way that glucose is first broken down into glyceraldehyde which subsequently undergoes reduction to glycerol (*c*) the union of fatty acids with glycerol is brought about through the agency of the enzyme lipase This catalytic action is reversible

Two possible sources are available for fat synthesis in the body glucose and protein Some of the amino acids of the naturally occurring proteins are convertible to glucose in the diabetic animal and since glucose can be transformed into fat it seems reasonable to assume that protein can be a precursor of fat It is not generally accepted that in normal healthy individuals fat is formed under conditions of excessive feeding of protein Normally fat is completely oxidised to CO_2 and H_2O in the body

Theoretically, 2 7 g of glucose may give 1 g of fat with the liberation of 0 55 g of water and 1 16 g of carbon dioxide, this transformation of carbohydrates into fat does take place even in the carnivorous dog (Morgulis and Pratt, 1913)

In the vegetable kingdom fats are synthesized from carbon dioxide and water under the influence of sunlight, probably via the intermediate formation of carbohydrates

Liebig (1852) pointed out that the fat of animals receiving a very similar diet was different according to the species, beef fat, for instance, being different in composition from mutton fat Fats are characteristic of the species (Lovern, 1935) Although fats are hydrolysed in the lumen of the intestine, their constituents are resynthesized in the wall of the intestine and carried in the chyle to the blood as neutral fats

Fats are found mainly in foods of animal origin, plants store their fat in their fruits and seeds, but fruits are generally not well supplied with it.

Smedley Maclean and Nunn (1940) believed that a minimum intake of arachidonic acid is necessary in order that the cells of the fat depots may first be loaded up with fat

Weight for weight, fat supplies about twice the energy of the other staple organic foods, carbohydrate and protein It is an essential in the structure and function of all tissues and especially of the brain and nerves (Bloor, 1942)

Fats serve passively as heat insulation under the skin, as padding to keep organs and blood vessels in place and for rounding out the contour of the body structure They constitute the most important form of stored energy

THE IMPORTANCE OF FAT

Mayer and Schaeffer (1913) and Terroine (1919) divide the fatty acids which are found in the body into two parts, an *élément constant* and an *élément variable* The former represents the fatty acid content of animals that have died of inanition It is independent of the individual and of the fat content of the animal at the beginning of the inanition period Within narrow limits it is constant for the species when expressed as a percentage of the body weight It is quantitatively and qualitatively constant in spite of all physiological variations The *élément constant* does not vary greatly in homeothermic or poikilothermic animals each considered as a class, but in the former it has a value about five times that found in the latter The *élément variable* which is the difference between the total fatty acid content and the *élément constant* exhibits great individual variations even in the animals of the same species The *élément variable* consists of those fatty acids which are present in the form of neutral fat and form the true reserve of fat of the animal, the *élément constant* is that part of the fatty acid which cannot be diminished in amount without causing death It is probably an essential component of the animal s protoplasm

THE ABSORPTION OF FAT

It has been generally thought that fat is absorbed only after being split up in the intestine by lipase into fatty acid and glycerol The fatty acid enters the mucosal cell with glycerol which is absorbed at the same time to re synthesize neutral fat This synthesis passes through an intermediate stage of phosphatide formation Probably the glycerol is phosphorylated and combines with the fatty acids (Fatty acids would be dangerous if absorbed in very large amounts and the re synthesis to neutral fat abolishes this danger) Two fat splitting enzymes are present in the intestinal content one being provided by the pancreatic juice and the other by the intestinal juice

The velocity with which fats leave the stomach is connected with their melting point and viscosity (Tangl and Erdelyi 1911 Fejer, 1913) Fats which are absorbed quickly seem to leave the stomach quickly

Frazer and Stewart (1937) stated that the lipaemia following a meal containing fat occurs within 1½ hours of ingestion reaches a maximum in 2–3 hours and the curve returns to the resting level in 4½ hours

Deficiency of vitamins A, B or D and anaemia causes a decrease in the rate of absorption of fat

The mechanism of fat absorption

Absorption of fat from the stomach

It is generally believed that fats undergo practically no digestive changes in the stomach This subject has been reviewed by Karel (1948)

Absorption of fat from the small intestine

The difficulty in explaining the absorption of fat arises from the fact that fat and fatty acids which are its elemental constituents are insoluble in water and therefore how they could pass through the epithelium of the intestinal mucosa Three different possibilities have been suggested (1) fat might be dissolved in the lipoids of the cells after splitting into fatty acids whilst the glycerol might be absorbed by its solubility in water (2) fat might be absorbed as an emulsion bile acting as the emulsifying agent the mechanism being one of filtration through the mucous membrane and (3) fat is saponified and is absorbed in the form of a water soluble sodium soap

That change in the diffusibility of fats and fatty acids through collodion membranes may be brought about by bile has been shown by Neill (1921) Mellanby (1927–28a) stated that the accepted hypothesis for the absorption of fat from the alimentary canal assumes (1) that fat is taken into the colum nar cell of the villus as fatty acid and glycerol (2) that re synthesis of fat occurs in these cells and (3) that neutral fat passes from the cell into the villus spaces and thence into the central lacteal

Verzar and McDougall (1936) have put forward the lipolytic hypothesis of fat absorption Frazer (1938) has suggested the partition hypothesis as distinct from the emulsification theory to explain the mechanism of fat absorption Bloor (1939) reaffirmed the hydrolysis theory According to

Frazer (1940) the lipolytic hypothesis must be regarded as unproven Frazer, Schulman and Stewart (1944) have shown that only the triple combination under the conditions prevailing in the intestine, of fatty acid, bile salt and monoglyceride is effective for fine emulsification (over the *p*H range of 6 0–8 5), adequate quantities of monoglyceride being formed during the first 5 hours of pancreatic lipolysis (Frazer and Sammons, 1945)

Comparing the lipolytic hypothesis of Verzar and McDougall and the partition hypothesis suggested by himself, Frazer (1946) stated that there is general agreement on the main changes which fat undergoes during absorption The occurrence of emulsification, hydrolysis and phosphorylation, and the importance of bile salts and the adrenal cortex are recognized by both groups of workers, the differences lie in the way these changes are brought about, and in their significance and relationship to the absorptive mechanism Frazer considered that the available evidence does not support the conception of the fat absorption mechanism which maintains that fat is completely hydrolyzed in the intestinal lumen, that the intestinal cell has an outer pavement membrane, that paraffins are not absorbed, that the adrenals control phosphorylation of fat in the intestinal cell and that no significant amount of fatty material passes up the portal vein during absorption In addition the lipolytic hypothesis provides no adequate explanation of the fine emulsification of fat in the intestinal lumen the differentiation between neutral fat and fatty acid absorption, the effect of added or inhibited lipolysis the difference between the absorption of tributyrin and long chain triglycerides, and the improvement in fat absorption when adrenalectomized animals are adequately salt treated Frazer (1952) concluded that there are two different forms, involving two different mechanisms and two different routes, by which the absorbed fatty material may pass into the body (*a*) the water phase, by *molecular* dispersion of short chain fatty acids and long chain soaps with passage into the portal blood and (*b*) the oily phase, by *particulate* dispersion of glycerides and long chain fatty acids and resynthesization to triglycerides with passage through the chyle into the systemic blood

Becker, Meyer and Necheles (1950) stated that the results of their investigations support the theory that fat may be absorbed in the unhydrolyzed state

DIETETIC CONSIDERATIONS

THE DIGESTIBILITY OF FAT

Holmes and Deuel (1920–21) studied the digestibility of three vegetable oils—cotton seed peanut and corn—which were partly hydrogenated in order to obtain hardened oils with different melting points They observed that as the melting point increased the digestibility decreased, this also corresponded to the iodine number which decreased with decreased digestibility It has been stated that the digestibility coefficient of fats with melting points above body temperature varies inversely with the melting point The critical

temperature above which there is a marked decrease in digestibility in man appears to be about 50° C Shorter chain fatty acids are more completely absorbed, the chemical constitution appears to be the important factor A natural emulsion (milk) is much better digested than emulsified or unemulsified fat

The characteristic aromas and flavours of the various fats are due mainly to the presence of non fatty materials, pure, fresh, glycerides of the higher fatty acids being odourless and tasteless Ease of assimilation depends to some extent on melting point liquid oils and the softer solid fats being almost completely digested, while fats which have been hydrogenated to a melting point of 50 C or above are utilized less efficiently Hilditch (1935) believed that absorption depends almost completely upon the possibility of the fat being liquid at body temperature

The lower the melting point, the more completely is the fat absorbed Fats which have melting points lower than the temperature of the body are digested more easily than those which remain semi solid in the alimentary canal The melting point is lower after recent melting, thus cooking may make certain fats more assimilable (Frazer, 1940) Plants and cold blooded animals (fish) have fats of low melting points Fats found in milk cream and egg yolk are the most easily digested because they are in the form of an emulsion

For practical purposes digestibility may be defined in terms of the inverse ratio of the gastric motor and secretory response produced by the food which corresponds to the time required for its evacuation from the stomach

Fat tolerance

The tolerance of fat varies from individual to individual but it is now generally recognized that many people show a distinct intolerance to fat, which is particularly marked in children who show a natural revulsion to it.

Porges (1929) has emphasized that peptic ulcer patients are unable to take oil after a short period of treatment Tidwell Holt, Farrow and Neale (1935) confirmed that premature infants and twins have a marked difficulty in fat absorption According to Jewesbury (1937) indigestion in breast fed infants is most likely caused by the high fat content of the milk

According to Cruickshank (1946) most people are aware of the disadvantage of too fatty a meal and he advises that for young children and those with weak digestions fried foods fat meats and pastries should be excluded from the diet

Reinhold (1948) has reported a case of fat indigestion in a breast fed infant the milk containing 7 4 per cent of fat, although the mother took very little fat in the diet

Young girls employed on machines in war factories which splashed fine particles of oil into the atmosphere have been found to be constantly ingesting the oil and having their clothes saturated with it This resulted in nausea in many cases and consequently the inability to eat a morning meal

Fat tolerance of the Eskimo

The Eskimo has been frequently mentioned as an example of great fat tolerance exhibited by people living in cold climates (Heinbecker, 1928) ("Eskimo" is derived from the Indian and means raw flesh eater)

Bilby (1923) stated that it is a common error of writers upon the Eskimo folk to assert that they oil themselves to keep out the cold, that they drink oil as a food and revel in grease generally—nothing is more inexact The Eskimo housewife uses a blubber hammer (a stone, or mallet of ivory tusk set in a wooden handle) to beat down the seal or whale fat into oil for her lamps Seal oil and melted blubber act as strong purgatives and cannot be used for internal consumption

Thomas (1927) reported on the opportunity of making a cardiovascular and renal survey of a group of people subsisting exclusively on meat which presented itself during the MacMillan arctic expedition of 1926, where he was in close contact with the Eskimos of northern Labrador and Greenland He stated that their diet includes the meat of whale, walrus, seal, caribou musk ox, arctic hare, polar bear, fox, ptarmigan, and the numerous sea birds geese, duck, auks gulls and a variety of others, and finally, fish, all eaten usually (and preferably) raw Contrary to general opinion, the Eskimo eats relatively little fat or blubber This portion is used for its oil, in lighting and warming the domiciles, melting ice and snow for drinking and for cooking

Drummond (1934b) thought that when a wider view is taken, it is recognized that the metabolic efficiency of the Eskimo is less a matter for surprise than the rather poorly developed powers of dealing with fat which our own race exhibits

Grenfell (1943), writing on the life of the Eskimo in Labrador, says that the high plateau has always been a home for the caribou, which has afforded the northern Indians an easier existence Given a mixed group of Eskimos from north of Cape Chidley and those from the south, nurtured around the Moravian Mission stations and relying on flour and 'civilized' diets, it would be possible for any intelligent stranger to separate them correctly, simply by the difference of their physique The Northerners are sturdier, livelier and have a true red colour in their cheeks

Mr and Mrs Manning (1941) exploring the arctic region mention specifically that blubber was used only for fuel

Father Buliard (1953) also emphasized that the Eskimo lives exclusively on meat The man kills the seal and the woman cuts out the blubber to keep the lamp filled with oil

Although Duncan (1947) does not specifically refer to gastric diseases, he thinks that the only plausible explanation of the immunity of an isolated colony in the far north Yukon territory against rheumatic fever, toxaemias of pregnancy and nephritis can be ascribed to the diet, which consists mainly of an unlimited quantity of wild meat

THE EFFECT OF THE FAT LEVEL OF THE DIET ON GENERAL NUTRITION

Burr and Barnes (1943) stated that high levels of fat in the diet produce in a short time the same result as low levels fed over a longer period

The brain is exceptionally constant in its fatty acid contents (due to the inability of the nervous tissue to burn fat or acetone bodies)

Crampton and Mills (1945) by feeding rats on isocaloric amounts of diets containing 4 per cent and 16 per cent of fat respectively observed that there was better growth on 4 per cent than on 16 per cent whether the animals were fed *ad libitum* or isocalorically Forbes Swift, Elliott and James (1946), who used four diets containing 2, 5, 10 and 30 per cent of fat respectively, and supplying the same quantities of gross energy, protein and vitamins found that the gains in live weight the digestibility of nitrogen and the retention of nitrogen and energy were in the order of increasing fat contents of the diets

Minimum fat requirements

Anderson and Williams (1937) have pointed out that standards of fat intake proposed by physiologists show wide variations as does the actual intake in various parts of the world

The fat consumption in different people varies greatly and is affected by the climate, by local habits and by the amount of work which has to be performed There is greater wastage in edible fats than in other edible foodstuffs (Halliburton 1918, Pearl 1920) According to Rubner (1902) 20 g of fat per head of the population appeared daily in the Berlin sewers

According to Hindhede (quoted by Starling 1919) a man can be kept alive and work normally on a diet in which fat is practically absent, provided the accessory factors are supplied in sufficient quantities The Japanese soldier appears to be satisfied with 20 g and the African Bantu with 30 g of fat per day (Hutchinson 1911)

Marrack (1942) has pointed out that since fat can easily be made in the body from carbohydrate and amino acids it is hard to see why it should be an essential in the diet and thus it is probable that fat as such is either not essential or is needed in small amounts only People of Eastern Europe drink practically no milk (Marrack 1942) According to Cruickshank (1946) there is considerable prejudice against the use of milk and butter by the Chinese Le Gros Clark (1948) pointed out that while a small quantity of fat is needed as a vehicle for the fat soluble vitamins it is doubtful whether fat otherwise plays an essential part in the diet

Drummond (1948) has emphasized that food habits are usually very deeply rooted and that it is important to recognize that there is a psychological aspect of the fat minimum question

In the report of the Committee on Nutrition published by the British Medical Association (1950) it is stated that the Committee is unaware of any

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changes leading to gangrene and necrosis, and loss of hair from the face neck and back The disease is cured or prevented by the addition of 2 per cent of fatty acids to the diet The nonsaponifiable fraction of fats and glycerol are ineffective Three drops of fat daily have a measurable effect

Funk Caspe and Caspe (1930–31) described a new pathological condition of probable dietetic origin in rats which differs from that described by Burr and Burr (1929) in that the segmentation of the tail develops earlier and is not prevented by lard, cod liver oil and linoleic acid Additions of vitamin B had some beneficial effect (Sinclair, 1930 1931, Hume and Smith 1931 Gregory and Drummond, 1932)

Gregory and Drummond (1932) observed that when they fed rats on a fat free diet to which they added 30 per cent of synthetic olein the growth was very poor, but that when they returned to a fat free diet the rats immediately commenced to grow again From the rapidity with which the decline of weight occurred when large amounts of fat were given, they concluded that a toxic substance was present

Graham and Griffith (1930–31) pointed out that in the effects produced by the basal diet of Burr with 0 5 g of whole dried yeast and 9 drops of cod liver oil the signs of the disease are prevented by wheat germ oil lard and whole liver, wheat germ oil being the most effective and lard the least

Burr and Burr (1930) found that the interference with growth, scaliness of the skin and the kidney lesions produced by a completely fat free diet were cured and prevented by linoleic acid, in an isolated pure state or as a constituent of olive oil, lard corn oil, poppy seed oil linseed oil or egg lecithin

Burr, Burr and Miller (1932) found that oleic acid was ineffective and classed it with the saturated acids but linoleic and linolenic acid were equally effective and interchangeable

Gyorgy, Sullivan and Karsner (1931) considered that the various nutritional dermatoses of the rat are clinically quite different vitamin H deficiency (egg white injury) vitamin B_6 deficiency (rat acrodynia) and lactoflavin deficiency can be produced and prevented

McKay and Barnes (1941) believed that there appears to be some similarity between egg white disease and the eczema described by Burr and Burr (1929) They found that egg white injury or acrodynia in the albino rat which occurs when commercial dried egg white is included in the diet of this animal in a substantial amount develops much more slowly if 10 per cent of the diet is in the form of corn oil which is rich in linoleic acid instead of lard If vitamin B is injected into corn oil fed rats the signs and symptoms of the egg white acrodynia disappear almost entirely

According to Burr and Barnes (1943) the goat cow chicken and pig have been kept for short periods on diets low in fat without the development of outward signs of the deficiency

Little appears to be known about the requirements of man for unsaturated fatty acids

evidence that there is a minimum daily intake of fat required to maintain the health and well being of the human body

It should be noted that in practice it is impossible to have an absolutely fat free diet unless the diet be prepared from synthetic ingredients Even the "leanest" natural foods contain in most cases a small percentage of fat The fat content (dry weight) for white bread is 1 9 per cent, for brown bread, 2 6 per cent, for oatmeal 9 per cent, for spongecake 13 per cent, for vegetables 1 5 per cent, for fruits 1–8 per cent (Lea, 1398)

Fat deficiency diets

Drummond (1920–21) stated that it would appear probable that the mammalian organism can exist without receiving fat in the food and that it would be reasonable to suggest that pure fats are dispensable constituents of the mammalian diet If true fats are essential for nutrition during growth the minimum necessary must be exceedingly small (Osborne and Mendel, 1920–21) Rats fed on a diet containing not more than 0 08 per cent of fatty materials develop and behave normally (Drummond and Coward, 1921)

Hill and Bloor (1922) have shown that fatty material was always present in the faeces, whether fat was present in the diet or not, and that the composition and properties of the excreted fatty material were largely independent of the fat of the food According to Sperry and Bloor (1924) almost as much fat appears in the faeces on a fat diet as on a fat free diet (confirmed on Thiry-Vella fistula dogs by Angevine, 1929) Fatty material of the faeces has its origin largely in the blood The effect of food is shown by a much greater lipoid excretion on a fat free diet than on fasting Sperry (1926) suggested that lipid excretion may be concerned with removing undesirable or excess sterols from the organism Bile is not the source of faecal lipids (Sperry 1926–27) Sperry (1929–30) showed that there was two or three times as great a lipid excretion by bile fistula dogs as by normal dogs. He separated the faeces into (1) bacteria (2) non bacterial solids and (3) soluble material and found that 40 per cent of the total fat excreted on "fat free" diets is in the bacterial fraction Gregory and Drummond (1932) found about 8 per cent of phospholipids in the faeces after a fat free diet, with a percentage of sterol at nearly 40 per cent

Unsaturated acids produce unsaturated fatty acids while neutral fat is synthesized from carbohydrates (Sinclair 1929)

McAmis, Anderson and Mendel (1929) found that while comparatively good but by no means optimal growth has been recorded the best growth was exemplified by those animals which received some small inclusion of fat in their diet Whether the apparent beneficial effect of a small amount of fat is due to its content of vitamin A or other vitamins or to its action as a vehicle for the fat soluble vitamins or whether fat *per se* is essential, is not conclusively demonstrated Burr and Burr (1929) described in the rat a deficiency disease which was produced by a diet of high purity, extremely low in fat, and was characterised by abnormal conditions of the skin, the feet and tail developing a scaly condition which was followed by inflammatory

not recurred The blood pressure 140–150/95–100 dropped to 130–85 after 4 or 5 months, but rose after resumption of the normal diet There was a loss of weight of about 14 lbs during the first 3 months which then remained steady There was a decrease in the serum fatty acids, 5 7–3 2 per cent in linoleic acid and 3 2–1 8 per cent in the arachidonic acid This indicated the probability that the normal human subject is unable to fabricate highly unsaturated fatty acids

The percentage contents of linoleic acid are as follows olive oil 7 per cent peanut oil 25 per cent sesame oil 35 per cent soya bean oil, 50 per cent hard lard 1–7 per cent oily lard 35 per cent egg fat 15–19 per cent (Jamieson 1932) hen fat 22 per cent beef tallow 3 per cent and mutton tallow 4 per cent (Hilditch 1935)

Low-fat diets

Deficiency of essential fatty acids has been blamed as the cause of certain cases of eczema in children

Hansen (1932–33) observed that the total iodine absorption values in eczema averaged 383 mg iodine absorbed per 100 cc of serum, while for the controls they were 539 mg Hansen (1933–34) confirmed his previous communications that the iodine number of the serum fatty acids was abnormally low in infantile eczema during the active phase of the disease and that oils rich in unsaturated fats improved the condition

Holt, Tidwell, Kirk, Cross and Neale (1935) observed three infants on a low fat diet, one developed eczema but there was a remission when fat was added Their blood lipid showed a moderate decrease in the degree of unsaturation of the serum fatty acids similar to that found by Hansen and Burr (1933 1937) and by Hansen (1937)

According to Burr and Barnes (1943) there was a moderate decrease in the iodine number of the serum lipids in two infants maintained at the University of Minnesota Hospital for 10 weeks on a diet extremely low in fat

Drummond (1948) quotes Macrae who investigated a number of children in an orphanage near Brussels soon after its liberation in World War II and who obtained evidence that a good diet caused the skin to become normal Merely increasing the quantity of fat, however, did not have the same effect

A most interesting experiment conducted on himself over a period of 6 months by one of the authors was described by Brown, Hansen, Burr and McQuarrie (1938) The diet of 2 500 calories was limited to sucrose, potato starch, baking powder sodium chloride ferric citrate, viosterol, carotene (vitamin A), orange juice citric acid anise oil, liquid petrolatum and milk practically freed of its fat The daily protein was derived from 3 quarts of milk and cottage cheese made from an additional quart of milk The chief source of fat was the skimmed milk which had less than 0 08 per cent of fatty acid content and represented 0 03 g of fat per kg of body weight per day Rats on this diet developed the characteristic symptoms of the fat deficiency syndrome in approximately the same time as Burr s rats The results observed were most striking The subject remained clinically well, without developing even a common cold during this period, one of the most notable subjective effects was the marked absence of fatigue The somewhat tired feeling usually experienced after a day s work in the laboratory disappeared within a few days from the institution of the diet It is also interesting to note that from childhood the subject had suffered from frequent attacks of migraine which had been occurring at intervals of 7–8 days immediately before the experiment After 6 weeks the attacks of headache subsided completely and had

Vitamin E

The source of vitamin E (the fertility vitamin) is wheat germ oil or hardened cotton seed oil—and neither of these oils contains vitamin A or D Meat eggs, green leaves and seeds supply vitamin E The examination of fats for vitamin E has shown it to be present in the unsaponifiable portion (Evans and Burr 1927) Weber Irwin and Steenbock (1939) found aerated lard (of a peroxide value of 11) destroys vitamin E as does exposure to sunlight, and it is made rancid by heating Moderately rancid fat destroys vitamin E

THE VITAMIN-SPARING ACTION OF FAT

Evans and Lepkovsky (1932b) suggested that fat is important in the diet because it has a sparing action on vitamin B Kemmerer and Steenbock (1933) found that a diet low in vitamin B_1 and high in fat did not affect the tissue content as compared with a diet low in vitamin and low in fat Sure (1932) found that the vitamin B requirements for lactation in the rat were not influenced by the amount of fat included in the diet, and he stated that a critical examination of the data of Evans and Lepkovsky does not justify the interpretation that fats have any sparing action on vitamin B requirements Gregory and Drummond (1932) and Drummond (1934b) also dispute their view

Anderson and Williams (1937) suggested that the vitamin sparing action of fat may be due to the actual presence of vitamin B in the fats Cowgill (1938) concluded from a review of the subject that vitamin B_1 is more likely related to carbohydrate than to fat metabolism Mannering Lipton and Elvehjem (1941) found that riboflavin requirements were increased with an increase of fat in the diet

THE PATHOLOGICAL EFFECT OF VITAMIN DEFICIENCY ON GASTRIC FUNCTION

Vitamin A

Diets deficient in vitamin A produce hypomotility of the intestinal tract (Gross 1924) The appetite is depressed and gastric acidity decreased (Wilbur 1939) The anorexia is not related to ulceration of the mucosa there is no change in the response of gastric secretion to histamine (Herrin 1940)

Vitamin B

McCarrison (1918–19) observed on pigeons and monkeys that the absence of vitamin B produces histopathological changes in the alimentary tract which frequently assume the clinical form of colitis Since he found degenerative changes in the myenteric plexus of Auerbach in animals on a vitamin B-free diet he concluded that the nervous control of the bowel was impaired in proportion to the degree of degenerative changes both in polyneuritic and scorbutic animals

CHAPTER 19

THE VITAMINS IN RELATION TO FAT

THE FAT SOLUBLE VITAMINS

Man can complete the synthesis of vitamin A from carotene, he can obtain vitamin K from the action of bacteria in his intestine and he can form vitamin D from the action of ultra violet light on the integument

Vitamin A

The growth promoting and antixerophthalmic vitamin A is most abundant in livers of certain marine fishes, in butter, cream, milk, egg yolk, and mammalian liver The normal human liver contains from 10–20 mg per 100 g of tissue Lard, almond oil, olive oil, and cotton seed oil do not contain vitamin A, but green vegetables contain comparatively large quantities of the vitamin Vitamin A in the livers of fishes and in milk depends on the food of the animal In the absence of air, vitamin A is not destroyed by heat In the ordinary processes of cooking, animal fats are exposed to air as well as heat and will, therefore, lose some of their vitamin A Butter and cream are the most palatable and assimilable sources of fat as well as carriers of vitamin A, but butyrin and ethyl butyrate are highly toxic. Vitamin A found in butter and cod liver oil is easily destroyed Heating and aerating them for a short time or exposing them for a longer time at room temperature deprives them of every trace of vitamin A (Mattill, 1927) Nuts cocoa butter vegetable oils lard and bacon while rich in fat are poor in vitamin A Excessive dietary fat which does not carry vitamins leads to a loss of vitamin A Rancid fats or stale diets are especially destructive of the A vitamins (Hickman, 1943)

Vitamin D

Vitamin D or the anti rachitic vitamin, is generally found in the same foods as vitamin A The richest source is liver of marine fish It affects fat metabolism since the presence of fatty acids in the intestine will prevent the absorption of calcium Ergosterol the precursor of vitamin D is a comparatively stable substance not affected by the preparation of foodstuffs

Vitamin K

This vitamin or the anti haemorrhagic vitamin, is found in animals only in the liver Vitamin K is fat soluble but it is contained in green alfalfa leaves cabbage, cauliflower spinach tomatoes and soya bean oil

increased motor activity as a result of diets high in yeast, while Allen and Burget (1928) observed that baker s yeast does not exert as great a secretagogue action as similar amounts of protein and fat

Williams Cox and Nash (1940) prepared a concentrated extract of fresh yeast which, when injected intramuscularly, stimulated gastric secretion in a histamine like manner They state that the tests which have been made suggest that while the active principle of the yeast extract is not histamine the evidence on this point must be considered as inconclusive According to Williams, Hoffman and Nash (1943) neurine (bromide) injected intramuscularly stimulates gastric secretion, the threshold dose of neurine base being 150 times larger than that of histamine

Vitamin C

Smith (1927a) has shown that there is no significant impairment of the gastro intestinal tract of the guinea pig in (experimental) acute and chronic scurvy

Plummer (1927) has observed that in the guinea pig with advanced scurvy the duration of spontaneous activity of the strips of intestine is decreased There is also a diminution in the number of rhythmic contractions except in the ileum where the reverse is true The increased amplitude of the rhythmic contractions indicated hypermotility in the colon and also a slight hyperactivity in the duodenal strip The tonus of the intestinal wall was considerably increased in the scorbutic strip

According to Webster and Armour (1934) vitamin C has no effect on gastric secretion in human beings These findings reduce the significance of the observations of Archer and Graham (1936) who have drawn attention to vitamin C deficiency in peptic ulcer and in haematemesis

Vitamin D

Bauer Marble Maddock and Wood (1931) have shown that the administration of irradiated ergosterol decreases gastric acidity in man and that the decrease is proportional to the amount of ergosterol used Webster and Armour (1934) observed no effect of vitamin D on gastric secretion while hypercalcaemia (Grant 1941b) and hypocalcaemia (Schifflers 1934) appear to depress gastric secretion

Cowgill, Deuel, Plummer and Messer (1926) have shown that avitaminosis B in dogs is followed by anorexia and gastric atony Feeding of vitamin B *complex restores normal conditions, but the systemic manifestations* characteristic of advanced cases of vitamin B deficiency suggest that the loss of desire to eat is due as much to a generalized systemic disturbance as it is to an abnormal condition localised in the alimentary tract

Gross (1924) has reported a decrease in intestinal motility in rats subsisting on vitamin B-deficient rations and Stucky, Rose and Cowgill (1928-29) found that vitamin B deficiency produces, in the majority of animals, a decrease in gastric motility Smith (1927b) has shown that dogs which have lost their appetite for vitamin B-deficient diets and show initial symptoms of beri beri have normal types of gastric hunger peristalsis Plummer (1927) has shown that absence of vitamin B from the diet of rats diminished the length of time during which an excised strip of intestine exhibits spontaneous contractions in oxygenated Locke s solution The amplitude and rate of the rhythmic contraction is markedly decreased in the spastic stage of the beri beri rats especially in the duodenal and ileal segments The tone of the intestinal musculature is also lessened

Rats kept on a B_1 deficient diet showed progressive gastro intestinal hypotonicity, dilatation and stasis (Gershon Cohen, Shay and Fels, 1938) In human beings with an abnormally long emptying time the period was shortened by administration of vitamin B_1 (Wood, Splatt and Maxwell, 1942)

The production of gastric achlorhydria in animals fed on diets lacking in vitamin B was shown by Webster and Armour (1932-33) First, diminution and then complete cessation of gastric secretion occurred but normal secretion was restored by the addition of powdered yeast to the diet Injection of histamine produced the free acidity of 0 409 per cent and total acidity of 0 536 per cent HCl while sham feeding and injections of 5 per cent alcohol into the duodenum showed the stomach to be apparently quite refractory to all stimuli The complete achlorhydria of avitaminosis was obtained independently of anorexia and manition, which never occurred in their experimental animals Wilbur (1939) showed that the deficiency of thiamine causes anorexia with concomitant decrease in gastric secretion, and there are some indications that a deficiency of thiamine or the vitamin B complex may result in inflammation and ulceration of the gastro intestinal tract

Avitaminosis B is followed by complete achlorhydria, and normal secretion is restored by the administration of yeast (Babkin, 1933, Webster and Armour, 1934) or by the administration of vitamin B_1 (Cowgill and Gillman, 1934, Schiffrin and Ivy, 1942) Contradictory reports have appeared on the action of vitamin B_1 on the stimulation of acid secretion in both dogs and man The pellagra factor apears to be different from the achlorhydria preventing factor In normal persons nicotinic acid has a histamine like effect

Comparison of records and direct observation of contractions of isolated segments of rat s intestine by Smith and Plummer (1928) do not indicate

reiterated in Exodus 34 25 "Thou shalt not offer the blood of my sacrifice with leavened bread neither shall the sacrifice of the feast of the passover be left unto the morning

THE DELETERIOUS EFFECT OF EXCESS OF FAT

While there is no evidence to support the view that a low fat diet has any deleterious effect on the body there is ample evidence to show that excess of fat has harmful effects and that there are many therapeutic indications for a low fat diet It is a matter of common experience that the addition of fat impedes digestion by remaining for a long time in the stomach fatty acids may also be produced (Ewald and Boas 1885)

Adler (1913) found that fat in the form of olive oil or cotton seed oil is toxic to rabbits Long-continued daily feeding of non toxic doses of oil produces blood crises resembling pernicious anaemia and extreme emaciation

Bloor (1913) quotes Ravenel who stated that bacteria have been shown to be aided in their passage through the intestinal wall by fats Fat acts as a culture medium for proteolytic bacteria High fat diets produce diarrhoea in some individuals and spastic constipation in others

Starling (1919) reported that a meal lacking in fat was deficient in staying power but this is contradicted by Christensen Krogh and Lindhard (1934) who in accordance with the observations of Krogh and Lindhard (1920) found a very pronounced difference in the capacity for work on different diets On a fat diet their subject would be able by the utmost mental effort to carry on for about 90 minutes when he would reach such a degree of exhaustion that he could no longer follow the metronome of the cycle ergometer On a carbohydrate diet two subjects were able to carry on over 4 hours and had to give up only through stiffness in muscles and joints Consolazio and Forbes (1946) observed 8 men for 9 days who put themselves on a high fat diet (pemmican) which contained a 71 per cent beef fat content Their morale deteriorated considerably and most of the men resigned themselves to semi starvation

It may be of interest to recall that Minot and Murphy (1926) prescribed a diet low in fat for the treatment of pernicious anaemia Higgins (1930) found that in the treatment of epilepsy by the ketogenic diet (high fat—low carbohydrate) the patients complain of some difficulty of doing hard and prolonged muscular work When the number of grammes of fat in the diet exceeds the number of grammes of protein and carbohydrate combined acetone diacetic acid and beta oxybutyric acid are formed (It should be noted that this method of treatment has now been generally abandoned)

Johnson and Freeman (1938) showed that the lymph collected during the digestion and absorption of fats is destructive to red blood cells the effect being maximal at the time when fat absorption was most rapid

Loewy, Freeman Marchello and Johnson (1942–43) found that the total bilirubin output was significantly higher on high fat diets than on calorifically equivalent low fat diets red blood cell destruction proceeds at a faster rate on a high fat diet than on a low fat diet

CHAPTER 20

THE DELETERIOUS EFFECTS OF FAT

THE DETERIORATION OF FATS (RANCIDITY)

It has been observed that frequently the preservation of a mixed food is largely a matter of the prevention of fat deterioration (Burr and Barnes 1943)

Evidence has been obtained that oxidized (rancid) fats, in addition to being inferior to the fresh material in palatability and nutritive value, may actually be injurious to health, and lead to digestive and other disturbances Whipple (1932–33) has found that dogs, fed on a diet containing oxidized fat, developed a disease which she termed the "oxidized fat syndrome , and ultimately died, while control animals, receiving a similar ration containing unoxidized fat remained in good health

The most important form of rancidity is that produced by the action of oxygen of the air on the fat

With the development of rancidity *in vitro*, natural anti-oxidants are used up and carotene and vitamin A are destroyed

In addition to the deleterious effect of oxidized fat on the vitamins in general, the detrimental properties of rancid fat induce nutritional deficiencies which are probably due to some direct activity in the body tissues Gyorgy, Tomarelli, Ostergard and Brown (1942) found that it destroyed linoleic acid They thought that such substances as lard, butterfat, or rice which have a procarcinogenic effect when given together with butter yellow (N N -dimethylaminoazobenzene) act by stabilizing the carcinogen either by reducing the unsaturated acid content of the diet or through an anti-oxidant effect They showed that the diet containing linoleic acid was very toxic and produced symptoms (loss of weight, anaemia, leucopenia) which could be prevented by the addition of yeast, the toxicity being due apparently to oxidation products of the unsaturated fatty acids Lavik and Baumann (1941), found that rancified fat was equally effective in tumour production as the skin application of 20 methyl cholanthrene Burr and Barnes (1943) found that a balanced diet to which pure vitamin B, cod liver oil and germ oil was added was very toxic the toxicity being related to the development of rancidity Gyorgy and Tomarelli (1943) found that yeast had anti-oxidant properties which were lacking in the B vitamins

It is interesting to note that the Bible gives a double injunction which has for object the avoidance of rancidity Exodus 23 18 prescribes that ' Thou shalt not offer the blood of my sacrifice with leavened bread, neither shall the fat of my feast remain all night until morning , and this injunction is

disorders designated as lipido es is a heterogenic collection of disorders To combine this group under the name "lipidoses has been generally accepted since fat like substances of different chemical constitution and properties are found which accumulate in reticulum cells and histiocytes

With the patient on a low fat diet the symptoms and signs of essential hyperlipaemia may promptly disappear, only to reappear with the resumption of an average or high fat diet (Movitt, Gerstl, Sherwood and Epstein, 1951)

A pathological manifestation of fat assimilation has been described by Williams (1907) This consists in the formation in the intestine of definite calculi containing insoluble calcium soaps of the higher saturated fatty acids, along with free fatty acids and calcium phosphate These concretions are met with in the form of intestinal sand calculi in the vermiform appendix or enteroliths large enough to cause intestinal obstruction Intestinal sand is found in greatest amounts in abdominal cases associated with colicky pains

Patients on a high fat low carbohydrate diet put on far less weight than those on a high carbohydrate low fat diet It is a matter of general observation that high carbohydrate low fats diets in conjunction with the administration of insulin give the most gratifying results in sanatoria for tuberculous diseases

The relation of fat to neoplasms

The occurrence of neoplasm in relation to the fat problem is of great interest

Leitch (1924) quoted Scott who has drawn attention to the large proportion of cancer amongst the workers of the Scottish shale refineries Leitch produced tumours in 30 out of 75 mice with various oils of the shale group by applying them repeatedly to the skin and this is well illustrated by the studies of the so called mule spinners cancer and the prevalence of cancer of the skin amongst the workers of the paraffin mines of Scotland

Further to the experiments of Yamagiwa and Ichikawa (1918) who produced papillomas by coal tar applications, Burrows and Johnston (1925) injected 1–5 cc of the pure sterile corn oil into the subcutaneous tissue the mass broke up but remained unabsorbed the lesions being similar to those produced by mineral oils and tar Burrows and Farr (1927) stated that cancer is directly the result of the removal of the excess of the ergusia (fat soluble vitamins) from local areas of the tissues They believed that mineral oils, tars and especially the animal and vegetable oils and fats which are largely free from fat soluble vitamins when introduced into the tissues induce cancer and crowd the cells by dissolving and removing the fat-soluble vitamins *from adjacent areas of the* tissues Their observations apply both to the skin and the intestinal canal Whipple (1932–33) who fed dogs with lard made rancid by oxidation produced loss of hair rash, loss of appetite black and hard stools—convulsions diarrhoea—death Roffo (1931) held that the soil in which a neoplasm appears is powerfully influenced by the lipoids There is an increase in cholesterol in pre-cancerous conditions in the tumours and the heliotropic quality of cholesterol the face being more sensitive than the uncovered skin Cholesterol becomes photo active under

According to Adlersberg and Ellenberg (1939) a high fat diet diminishes the uric excretion in normal individuals

French (1942) observed that the most efficient calcium utilization was obtained from a diet containing 1 g of fat to 0 06 g of calcium and that the utilization decreased consistently in the order of the increasing fat content of the diets from 5 to 28 per cent, and then considerably for the 45 per cent of fat diet

Simple excess of fat in the diet can easily be shown to cause an increase of fat deposition in the liver (Frazer, 1940) Drosd and Crohn (1942) stated that a high fat diet produces a coated tongue and bad breath They suggested that the true or essential halitosis depends probably on some fault in fat digestion and its intestinal absorption and splitting, or, perhaps in some fault in the hepatic reassembly of fatty acid radicals and soaps with newer equivalents of sterol and fats in man

It is well known that skin diseases are improved by low fat diets Sutton and Sutton (1939) have prescribed it for the treatment of acne, Barber (1939) for seborrhoeic conditions and Bigham (1941) for chronic psoriasis

The rat tolerates fat extremely well (Hoagland and Snider, 1940) but it is difficult to relate the results of experiments on rats to the fat tolerance in man Catel (1936) attempted to feed rats on an exclusively fat (butter) diet, but the experiment had to be abandoned because the animals refused it after a few days

Douglas-Wilson (1944), studying the somatic manifestations of psychoneurosis in the Services, noted that the patients attributed the progression of their symptoms to greasy food

Following epidemiological studies of Swank (1950) which suggested the possibility that the incidence of multiple sclerosis in different geographical areas varies directly with the amount and type of fat intake, Wilmot and Swank (1952) attempted to determine whether this relationship was one of cause and effect or merely coincidence They could find no essential differences between normal subjects and patients with multiple sclerosis with respect to either lipid levels or the response of lipid levels to the change of diet which for long periods contained 20–50 per cent of the fat normally consumed

Major disturbances in the metabolism of lipids associated with the accumulation of lipids in the reticulo endothelial cells may be classified as follows (Moore, 1944)

I	Cerebrosis lipoidosis	— Gaucher s disease
II	Phosphatide lipoidosis	— (a) Niemann Pick disease
		(b) Amaurotic family idiocy
III	Cholesterol lipoidosis	— (a) Xanthomatosis
		(b) Hand Schüller Christian disease
	Disturbance in absorption	— Lipodystrophy (Whipple's disease or intestinal lipodystrophy)

According to Thannhauser and Schmidt (1946) the group of metabolic

are used as solvents He emphasized that there is abundant evidence that diets high in fat tend to increase the rate of formation of certain types of induced tumours

Lushbaugh (1946–47) exposed rhesus monkeys to the vapour of shale oil Hyperplastic gastritis polyps and penetration of the submucosa by epithelial growths were found in 2 monkeys that survived the longest One monkey that lived 1½ years was found to have severe atrophic gastritis

Kirby (1945) who attempted to induce stomach tumours by the administration of cholesterol esters heated at 300 C and of cholesterol heated at 430 C was unable to confirm Roffo s results Grossman and Ivy (1945) believed that in relation of diet to cancer there may be a local effect produced by fat

Roffo (1946) confirmed his earlier work which showed the role played by the cholesterol derivates in the cancerization process as it also demonstrated that the cholesterol which has been oxidated by heating or by the action of ultra violet rays undergoes physiochemical and biological changes which confer to it the value of a carcinogenic agent since its ingestion induces cancerous lesions in the stomach In his experiments on white rats fed on an ordinary diet of soup or milk bread and bran to which 1 cc of boiled sun flower was added Roffo observed that during the first months the general condition and weight of the animal improved but that mortality began to be observed after the sixth month of the new diet Roffo suggested that the carcinogenic action of heated pure olive oil and animal fat is due to formation of oxycholesterol by heating and that the common factor between many carcinogenic agents is the central phenanthrene nucleus of cholesterol

Peacock (1947) reaffirmed that methods of cooking which involve heating fats and oils to temperatures about 300 C provide a source of potential carcinogens

Ivy (1955) who confirmed Roffo s experiments concluded that the over heated fat (lard heated at 350 C for 30 minutes) contained low grade carcinogen

Sako (1942) found a lowered resistance to pneumococci in mice which had received a high fat diet (50 per cent) for 6 weeks as compared with animals fed with less (25 per cent) A high fat low protein diet caused the highest mortality and lowest survival period to dogs exposed to benzene fumes (Li Freeman Hough and Gunn 1945–46) whilst rats exposed to benzene and maintained on a high fat diet manifested a greater incidence of leucopenia than the control groups, irrespective of the protein content of the diet (Li and Freeman 1945–46)

Diabetes

The relation of fat to diabetes is of great practical importance because it is generally overlooked that the consumption of fat has considerable influence on carbohydrate intolerance The significant clinical observation has been made that diabetics do better on diets which are restricted in fats Diabetics who were treated on a high fat diet—before the advent of insulin—looked

the influence of sunlight, x rays, ultra violet light and radium and retains this property for 9 or 10 days after exposure Domagk (1938) found that there was a greater incidence of gastric carcinoma in butchers, publicans and waiters He quoted Liek who stated that in India 4 per cent of carcinomas are situated in the alimentary tract but the incidence approached 60 per cent in Denmark He considered that oils and fats, not only animal but vegetable, are the probable cause of the considerable number of carcinomas of the stomach and intestine He reported a gastric adenocarcinoma in 1 of 20 mice fed on a diet of rice and 20 per cent olive oil alternating each week with the usual diet for one year Roffo (1938–39) claimed to have obtained a wide range of pathological lesions, including ulcer, papilloma and carcinoma of the fore stomach, adenocarcinoma of the glandular stomach and sarcoma of the stomach and liver, in rats fed with heated or ultra violet radiated cholesterol and with overheated animal and vegetable fats

Klein and Palmer (1940) considered that the lesions produced by Roffo did not meet accepted criteria for malignancy because the lesions were limited by the serosa and no metastases were observed, it was not shown that they were irreversible in the absence of the stimulus, they were not transplanted and there were similarities to less severe and non malignant lesions observed under other conditions

Beck and Peacock (1941) confirmed Roffo's experiments They concluded that "the heated fats did not contain recognizable amounts of any known carcinogens but they included some substance which interferes with the antimony trichloride reaction for vitamin A, giving a bright red coloration' Rats fed with repeatedly heated fats in addition to a diet rich in vitamin A (carrot) showed no gross pathological lesions in the fore stomach or reduction in liver vitamin A (presence of "anti vitamin A of undetermined nature')

According to Peacock (1943) the preference of carcinoma for the pyloric end of the stomach, often stopping abruptly at the pyloric valve, is compatible with the conception of the regurgitation through the pylorus of a bile soluble carcinogen which is activated by the acid *p*H of the stomach He considered that Bonne's observations rather suggested that the same or associated factors induce either ulcer or cancer, depending on individual susceptibility

According to Wierda (1943) it was taught that diverticula of the colon is restricted only to man and that it occurs only in the latter half of the life span In 3 rats which were fed a high fat diet for 90–111 weeks, one or more diverticula of the colon developed in each In appearance the diverticula resembled the type found in man, and seemed to be the result of high pressure within the intestine acting against a specific limited area of the wall Morris Larsen and Lippincott (1943–44) observed white nodular elevations of the gastric mucosa (benign papillomas) after feeding heated lard to rats There were also chronic gastric ulcers with atrophic epithelium at the edge of the ulcer cirrhosis of the liver and lesions of the heart and kidney

Rusch (1944) has pointed out that the incidence of tumours is high following the subcutaneous injection of carcinogens dissolved in vegetable oils whereas fewer neoplasms are produced when fatty extracts of animal tissues

in western countries has been associated with an increasing consumption of fat The higher incidence in urban as compared with rural populations and the increasing incidence with financial status are both correlated with the amount of fat consumed

Atherosclerosis

Atherosclerosis of the aorta and its branches by far the commonest vascular disease ranks high amongst the causes of natural death in man Rabinowitch (1930) believed that excess blood cholesterol is an important aetiological factor in the production of arteriosclerosis in the young diabetic but Man and Peters (1935) found severe arteriosclerosis with or without hypertension evident in patients with serum cholesterol normal below normal or above normal

Duff (1935) gives a detailed review of experimental cholesterol arterio sclerosis He stated that arterial lesions which resemble those of arteri sclerosis in man can be produced in rabbits by the administration of diets containing considerable quantities of cholesterol with a resulting elevation of the level of cholesterol and other lipoids in the blood

Duff (1936) recognized the importance of hyperlipaemia but believed that the deposition of the lipoids in the walls of the arteries takes place only after the occurrence of a primary injury to the walls of the vessels Joslin (1937) stated that when diabetics were treated with high fat diets radiological evidence of arteriosclerosis could be found in many juvenile diabetics

That the serum cholesterol level is significant in relation to the develop ment of atherosclerosis is now well established Davis Stern and Lesnick (1937–38) found the average cholesterol free and total lipid phosphorous and fatty acids in a group of patients with angina pectoris of atherosclerotic origin higher than in a group of control subjects These observations have been confirmed (Gubner and Ungeleider, 1949 Duff and McMillan 1951 Gould 1951 Keys, 1951a, b Katz 1952) Similar observations had been made for New York by Page Kirk Lewis Thompson and Van Slyke (1935) for Southern Minnesota by Barker (1939–40) for San Francisco by Collen (1949) for Boston by Gertler Garn and Bland (1950) and for Denmark by Kornerup (1950)

Hirsch and Weinhouse (1943) stated that although no generally acceptable cause for the lesions has been established and while some regard it as an ageing process of the vessels dependent on focal changes of the media (Vir chow Sanders Beitzke Wells) there is evidence in favour of the view that it is due to lipid infiltration of the intima as a result of disordered lipid meta bolism (Marchand Lubarsch Aschoff Antischkow Leary) The simple fatty deposits with atherosclerosis have the same lipid composition as the blood plasma and the normal intima This strongly suggested that the lipid deposits in atherosclerosis result from a non selective deposition of the plasma lipids

Moreton (1947–48) believed that atherosclerosis is produced by alimentary hyperlipaemia that high fat meals induce hyperlipaemia and that the size

asthenic and tended early towards the development of ketosis Reduction of their fat intake increased their carbohydrate tolerance

Sansum, Blatherwick and Bowden (1926) referred to the well known fact that diabetes occurred frequently among fat people and that the blood sugar can be raised by giving a high fat diet just as it may be by giving a high carbohydrate diet

Adlersberg and Porges (1926, 1927, 1928) suggested for cases of mild and medium diabetes a diet rich in protein and low in fat which improved carbohydrate tolerance, they argued that with a high fat intake so much fat is stored in the liver that the latter organ is unable to deal with carbohydrate Sweeny (1927) found in normal subjects that on carbohydrate diet the sugar tolerance curve after glucose rose from 0 08 to 0 12 per cent, on a protein diet from 0 62 to 0 16 per cent, on a fat diet from 0 065 to 0 19 and in starvation from 0 08 to 0 20 per cent It should be noted that during starvation the liver accumulates fat

Rabinowitch (1930) drew attention to the benefit derived by diabetics from a high carbohydrate low fat diet Nixon (1930) has pointed out the advantages to the diabetic of a diet rich in carbohydrates and low in fats Similar views were held by Dyke (1932), Graham, Clark and Robertson (1932), Barach (1932), Czoniczer and Kolta (1932), Jamieson (1932), Lawrence (1933), Gray and Sansum (1933), Geyelin (1935), and Man and Peters (1935)

According to Himsworth (1934a) a high fat diet reduces the sensitivity to insulin He suggested (Himsworth, 1935–36) that a diet relatively high in fat which produces a loss of carbohydrate tolerance predisposes to diabetes mellitus This view is supported by Joslin (1937) and by Treadwell (1942, 1946) who observed that hyperglycaemia follows in every case on a high fat diet and now prescribe as a routine low fat diets

Greene and Swanson (1940–41) observed that the glucose tolerance was improved with a high carbohydrate diet and diminished with a high fat diet Treadwell, King, Bebb and Tidwell (1942) noted that the most marked decrease in glucose tolerance was observed in animals receiving a diet which was high in fat and low in lipotropic factors Consolazio and Forbes (1946) who studied the effects of a high fat diet in a high temperature environment found that it decreases sugar tolerance

Houssay and Martinez (1947) observed that the toxic and diabetogenic action of alloxan increases in rats fed a low protein diet and even more in the case of a high lard diet or ox fat diet

The observation by Young (1949) on the state of the German diabetics who were subjected to extreme food shortage during World War II, supports the conclusions of Himsworth (1949a) that food restrictions as such but more particularly the restriction of fat, is responsible for the fall in the incidence of diabetes and diabetic mortality which was observed in England during the periods of food rationing Himsworth (1949b) has pointed out that the fall in the incidence of diabetics aged over 45 years parallels in a surprisingly consistent manner the reduced consumption of fat during the two periods corresponding to World Wars I and II and that the rise over the last 50 years

Katz (1952) concluded from a review of the history of experimental atherosclerosis that man, the chick and the duck develop atherosclerosis spontaneously Experimentally it is easy to produce gross atherosclerosis in rabbits or chicks it is more difficult in guinea pigs hamsters and ducks, and impossible in rats Schlichter (in Katz s laboratory) suggested that it may depend on species variability in lipid metabolism

Keys (1952) and Gofman Jones, Lyon, Lindgren Strisower, Colman and Herring (1952) suggested that a substantial measure of control of the development of atherosclerosis and myocardial infarction in man may be achieved by control of the intake of fats

Keys Fidanza Scardi and Bergami (1952) reported that in the year 1949 fats supplied 38 per cent of the calories in the United States of America, 34 per cent in Denmark and 32 per cent in the United Kingdom Studies of actual intake in working class families in England gave an average of 35 per cent For the whole of Italy the average was 20 per cent, and in the men surveyed by them in Naples it had the same value In 84 clinically healthy *men in Naples of ages ranging from 18–54 years the serum cholesterol level* conformed to the English and American age trend as far as the early thirties but did not increase thereafter They concluded that these facts probably have a bearing on the development of atherosclerosis and the incidence of coronary artery disease since they had the unanimous judgment of the local physicians that coronary artery disease is less common in Naples than in the United Kingdom and the United States of America Similar observations were made for Portugal, and by inference for Spain (Keys 1953)

Fullerton Davie and Anastasopoulos (1953) observed that alimentary lipaemia increases the coagulability of blood as measured by the accelerated clotting time and the clotting time in silicone coated tubes and they suggest that this provides the link with the high serum-cholesterol levels in the development of atherosclerosis

Keys (1953) concluded from a review of the subject that the concentration of total cholesterol in the blood serum bears an important relationship to the development of atherosclerosis and its sequelae and related clinical conditions The total cholesterol concentration in the serum of men habitually on diets characteristic of the United States changes directly with changes in the total fat content of the diet For the 40 years of records available, the proportion of fat calories in the total American food consumption has steadily increased On the basis of comparisons with other countries at present this rise in fat consumption might be predicted to be associated with an increase of the order of 50–100 per cent in mortality from degenerative heart disease for men aged 40 to 65

[Experimental atherosclerosis has been comprehensively reviewed by Katz and Stamler (1953)]

Bronte Stewart Keys and Brock (1955) who studied 383 men aged 40–58 residing in the Cape Peninsula found that coronary disease was rare in the Bantu commoner in the Cape negro and most common in those of European descent Highly significant differences were found in the mean total choles

of the lipid particles is comparable to that of the particles which are known to produce arteriosclerosis experimentally

Plotz (1949) pointed out that there is considerable evidence of a relation between coronary atheromatosis and cholesterol metabolism In a group of 10 patients suffering from coronary artery disease 9 had peptic ulcer, they all died within 7 months after being placed on a high fat diet Malmros (1949) attributed the reduction in the mortality from coronary thrombosis in the Scandinavian countries during World War II to the rationing, especially of fat Closs and Dedichen (1949) confirmed these observations

In children the cholesterol concentrations are lower than in adults

Keys (1949) found, in a study of clinically healthy men in Minnesota, a distinct difference in the average serum cholesterol levels between young (18–25 years) and middle aged (45–55 years) men Keys, Mickelsen, Miller, Hayes and Todd (1950) in 1,492 men (17–78) and 564 women (17–30) found no significant different averages in the concentration of cholesterol in the blood serum between the ages of 17 and 30, over this age there was an average increase per year of age of 2 2 mg of total cholesterol per 100 ml of serum

Gertler, Garn and Bland (1950a, b), in 146 working males and 95 males who had experienced myocardial infarction prior to the age of 40, found that at every age level between the third and sixth decade the coronary disease group had markedly higher and more variable serum cholesterol levels than the healthy group and that the ratio of serum cholesterol to serum phospho lipids remain highly correlated No advantage was gained in lowering cholesterol intake in coronary arterial disease

Tanner (1951) showed that in 46 relatively young men in England there was a mean annual rise of 1 7 mg per 100 ml There is no relation at any age between the serum cholesterol level and the habitual dietary intake of cholesterol (Keys, 1949, Keys Mickelsen Miller and Chapman, 1950, Gertler, Garn and White, 1950, Wilkinson Blecha and Reimer, 1950), while profound changes are produced by the intake of fat (Keys, Mickelsen Miller and Chapman, 1950, Keys, 1952) even when both caloric and cholesterol intakes are constant Hildreth, Melinkoff, Blair and Hildreth (1951) reported that 3 of the (male) authors subjected themselves to strict diets for 3–8 months They found that a reduction of the dietary fat produced a significant fall in the serum cholesterol concentration Addition of vege table fat produced a rapid significant rise of serum cholesterol to the levels observed before fat restriction

Feldman and Morrison (1951) found in a survey of 1,522 autopsies 101 cases (6 6 per cent) of peptic ulcer The incidence of peptic ulcer was 9 per cent among the 733 patients with arteriosclerosis of the coronary arteries and 10 5 per cent in the 152 patients with coronary occlusion

Adlersberg (1951) postulated from a genetic analysis of families with xanthomatosis and families of patients with coronary disease that early coronary atherosclerosis may be an hereditary disturbance of lipid metabolism manifested by elevated cholesterol levels and transmitted as a dominant trait

Frazer Stewart and Schulman (1942) reported that considerable absorption of liquid petrolatum from the intestine can occur if the oil is emulsified

In view of the considerable increase in the use of mineral oil in foods the Council of Foods and Nutrition (1943) has drawn attention to the evidence obtained from studies of the effects of the ingestion of mineral oils which show conclusively that its harmful potentialities are greater than had been supposed

Most unrefined mineral oil contains small amounts of undesirable by products and in some carcinogenic substances have been identified

Becker (1952) concluded from a review of the subject that there can be no single doubt that mineral oil and its emulsions should never be used internally'

The toxicity of cod liver oil

Scandinavian workers have claimed that cod liver oil may exert a harmful effect when administered over long periods of time Agduhr (1926) described pathological changes produced by the oil when given in doses as low as 0 1 cc. per kilogm per day Goetsch and Pappenheimer (1931) showed that rabbits and guinea pigs developed a characteristic muscular dystrophy when fed on diets that were heated with ferric chloride containing lard and cod liver oil. Bell Gregory and Drummond (1933) have shown that large amounts of cod liver oil causes retardation of growth of the albino rat and Madsen McCay and Maynard (1933) that it increased the rate of development and early severity of the muscle degeneration According to Clausen Barnes and Burr (1943) cod liver oil rapidly destroys vitamin E in mixed diets According to Komarov and Komarov (1940) cod liver oil when administered daily exerts a cumulative inhibitory effect on the activity of the gastric glands.

Richter (1942–43) tested over 1 000 children between the ages of 5–14 years simply by letting them taste a small spoonful of unadulterated cod liver oil progressively with increasing age more and more of them manifested a dislike for it. Rats kept on diets deficient in vitamins A and D responded in much the same way Carton and Naftalin (1953) reported massive oedema (exudative diathesis) in pigs fed on a diet rich in cod liver oil which resembled the exudative condition induced in chickens fed on high fat diets deficient in vitamin E as described by Dam (1944)

CONCLUSIONS

A review of the subject shows conclusively that only the addition of a minimum of fat is required because even lean foods contain a certain amount of fat which is sufficient for the requirements of fat soluble vitamins The lean meats average a contents of 5 per cent bread 1–2 per cent vegetables and fruits vary from 1 to 8 per cent (Lea 1938)

There is little fat available in primitive life where animals are hunters or are hunted and where constant exertions provide little opportunity for the deposition of a reserve of fat In the arctic regions man consumes more fat

terol level and particularly of the beta lipoprotein fraction of the serum The Bantus had the lowest levels, the Europeans the highest, the Cape coloureds were in between The fat consumption of the Europeans is more than twice that of the Bantu, with the coloured group intermediate Vogelpoel and Schrire (1955) confirmed electrocardiographically (5,004 examinations) that the incidence of myocardial infarction was uncommon in the Bantu (2–0 4 per cent), more common in the Cape coloured than in the Bantu (100 –18 1 per cent) and more common in the European than in the Cape coloured (448–81 5 per cent)

Kuo and Joyner (1955) noted that by following the hour to-hour post prandial lactescence levels in patients with coronary artery disease the attacks of anginal pains would invariably occur at or near the peak of the lipaemic curve

Mineral oil

According to Bloor (1913) petroleum hydrocarbons and unsaponifiable esters (wool fat) were found not be absorbed Burrows and Farr (1927) have shown that rats were unable to utilize the vitamin A of butter fat when the latter was mixed with liquid petroleum

Channon and Collinson (1929) reported that small traces of mineral oil could be absorbed by animals and deposited in the liver

Jackson (1931) repeated the experiments of Dutcher, Ely and Honeywell *(1927)* and *found vitamin A deficiencies when the butter fat and the liquid* petroleum were mixed but little difference when they were given separately The reason for this distinction was not apparent until Moore (1929) showed that carotene and vitamin A were separate substances

Curtis and Horton (1940) suggested in view of Moore's findings, that because of the preferential solubility of carotene in mineral oil, a sufficient amount of vitamin A should be taken with or dissolved in mineral oil whenever it is used as a cathartic or food substitute Curtis (1942) calculated that one ounce of mineral oil at body temperature is able to dissolve 140,000 international units of carotene and at room temperature, *120,000 units (The* ordinary daily diet provides 5,000–10 000 international units of vitamin A)

Todd, Dittebrand, Montague and West (1940) supported the view that excessive dietary fat which does not carry vitamins leads to a loss of vitamin A, so that one must refrain from the indiscriminate use of liquid paraffin

Smith and Spector (1940) found that mineral oil ingestion interfered with the utilization of vitamin D fed separately as cod liver oil to such an extent that 3 times as much cod liver oil was necessary to heal rickets in rats when the basal diet contained 5 per cent mineral oil, when the diet contained *10* per cent of mineral *oil 5–10* times more *cod liver oil was needed* to heal rickets According to Elliott Isaacs and Ivy (1940) and Javert and Macri (1941) the mineral oil interferes with the absorption of vitamin K

Morgan (1941) described a syndrome of mineral oil poisoning', with anorexia, indigestion, flatulence, fatigue nervousness, dyschezia and anal leakage, accompanied in many cases with considerable loss of weight

PART V

CLINICAL CONSIDERATIONS

This part deals with the practical approach to the problem The various aspects of the incidence are reviewed, hints are given as to the diagnosis and differential diagnosis, the orthodox medical and surgical treatments are critically reviewed before giving details of the author s original method of treatment

because it is a useful vehicle to provide in small bulk the enormous number of calories which he needs for his daily energy output

All animals refuse fat Domestic animals as well as tropical fishes eschew it completely Rats fed exclusively on fat refuse it after two days Humans are coaxed by gastronomic subterfuges to accept it Children show an instinctive revulsion to it In the nursery they are taught that "Jack Sprat could eat no fat, his wife could eat no lean"[1] There is no evidence that fat tolerance can be acquired

The indigestibility of fat has been recognized by the earliest observers Aristotle in his *Problemata* (quoted by Shay, Gershon Cohen and Fels, 1939) suggested that it was indigestible because "it swims in the stomach The best digestion takes place at the bottom of the stomach, where the fat does not descend"

The Bible gives very emphatic and repeated instructions on the subject

"It shall be a perpetual statute for your generations throughout all your dwellings, that ye eat neither fat nor blood (Lev 3 17)

' Speak unto the Children of Israel, saying Ye shall eat no manner of fat, of ox, or of sheep or of goat ' (Lev 7 23)

Robert Graves (1946) commenting on "sacrifice of prosperity ', makes it clear that the meat only was accepted by the Priest for his consumption The injunction, frequently reiterated, to "burn the fat as a sweet savour unto the Lord" (Lev 1 9, 6 15, 7 31, 8 21, 17 6) is clearly directed to the use of fat for the purpose of cooking and so, improving the taste and the digestibility of meat, this interpretation is consistent with Rashi s commentary on the relevant text

There is no condition which requires the administration of fat, there are many in which it is contraindicated The lean individual (*pace* Julius Caesar) has many mental and physical advantages, over the fat one, he generally feels fitter

Fat is the artificial product of a sedentary civilization

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THE INCIDENCE OF PEPTIC ULCER

THE INCIDENCE OF PEPTIC ULCER IN ANIMALS

It is generally agreed that chronic peptic ulcers do not occur spontaneously in animals These observations were made in the dog by Turck (1906) Mann (1916) Greggio (1916), Ivy (1919), Rogoff and Stewart (1926) Overgaard (1934) Volini Widenhorn and De Feo (1938), in the rat by McCarrison (1931), Howes and Vivier (1936), in the rabbit by Ophuls (1906) Beazell and Ivy (1936), in the monkey by Hoff and Sheehan (1935) Watts and Fulton (1935) The few references which report spontaneous ulceration in animals refer to the acute ulcer of infective origin (Keller 1936) Chronic lesions are produced by physical trauma Schroeder and Wegeforth (1935) observed in seals and sea lions chronic ulceration produced by sharp stones swallowed for trituration of food which were deeply embedded with nematodes

GENERAL INCIDENCE

The incidence of peptic ulcer is obviously of considerable importance but the statistics on the subject are confusing the difficulty arising from the lack of differentiation between the acute and the chronic lesion, perforation and the mortality rate and the presence of scars being usually taken as the basis of the statistical computations Dyspepsia is one of the most common of the unpleasant experiences to which man is subject About 50 per cent of 10 000 patients between the ages of 30 and 60 years, seen by Rivers and Ferreira (1938) complained of varying degrees of digestive difficulties

Although it is generally agreed that the incidence of both acute and chronic ulcer is increasing it must not be assumed that the increase in both varieties of ulcer is necessarily due to the same causative element

Necropsy reports

Brinton (1857) in 7 226 necropsy records found approximately 5 per cent peptic lesions Perry and Shaw (1893) in 17 652 records only 0 4 per cent Hart (1918) 11 per cent in 1 531 records Musa (1922) 12 per cent in 955 Holzweissig (1922) 6 9 per cent in 3 508 Robertson and Hargis (1925) 12 per cent in 2 000, Lehman (1926) 20 per cent in 1 000 Sturtevant and Shapiro (1926) 2 per cent in 7 700 Hurst and Stewart (1929) 11 per cent Portis and Jaffe (1938) 457 in 9 771 cases Gordon and Manning (1941) 2 7 per cent in 22 956 Gauss (1948) 5 per cent

Ivy, Grossman and Bachrach (1950) subscribe to the view that autopsy reports can be grossly misleading

Admissions to hospital

In respect of admissions to hospital the incidence of peptic ulcer was for Friedenwald (1912) 7 8 per cent in 12,598 patients, for Eusterman and Balfour (1936) 12 2 per cent of duodenal ulcer in 15,985 patients De Bakey (1940) in 544,801 hospital admissions had 2,607 cases of peptic ulcer (0 478 per cent) In a collected series of 1,193,916 hospital admissions the ulcer cases were 7,859 or 0 658 per cent Tidy (1941) found that there has been an enormous increase in gastro-duodenal disease in recent decades Rothe (1941) found that in Germany during the first two war years the total number of examinations increased and the percentage of positive findings also increased Markoff (1943), in a series of collected cases from 41 Swiss hospitals, showed that general admissions for 1932–42 increased by one third but were double for peptic ulcer admissions

According to Patterson (1944) 12 per cent of Americans are subject to peptic ulcer during some period of their lives Duodenal ulcer is four times as prevalent as gastric ulcer and also occurs earlier in life than does gastric ulcer Emery (1946) found that approximately 9 per cent of patients sought relief from gastro intestinal symptoms and 50 per cent of these patients had organic disease in the accepted sense of the term According to Ivy (1946) 10 per cent of the population will develop peptic ulcer during their life time Craig (1948b) stated that gastric ulceration was uncommon until the beginning of the nineteenth century, and that there is little evidence to suggest that duodenal ulceration was other than a rare disease until about the beginning of the present century Since that time there is evidence of a considerable increase in the incidence of duodenal and gastric ulcer in males Although gastric ulcer in females has become very much rarer, investigations point to an increase in the frequency of duodenal ulcer White (1951) concluded that there is still considerable confusion and difference of opinion on the subject of the incidence of peptic ulcer

Alsted (1953) carried out two surveys, in October 1940 and in October 1948, in order to ascertain the incidence of active peptic ulcer in the Danish population In 1940 an overall ulcer rate of 11 per 10,000 inhabitants was found, 16 8 per 10 000 males and 5 4 per 10,000 females In 1948 the corresponding figures were 16 9 per 10,000 inhabitants 27 1 per 10,000 males and 6 9 per 10 000 females The highest incidence up to 63 4 per 10,000 was observed amongst males between the ages of 40 and 55 years The male preponderance was more pronounced in 1948 than in 1940 The incidence of gastric ulcer rose by 300 per cent in males between the ages of 40 and 50 years, whilst the incidence of duodenal ulcer was only doubled

THE DUODENAL-GASTRIC ULCER RATIO

The duodenal gastric ulcer ratio was found to be 3 1 by Moynihan (1912) 1 1 by Morley (1913), 2 1 by Hart (1918) 4 1 by Mayo (1921), 2 1 by

Musa (1922), and 2 4 1 by Lehman (1926) According to Robertson and Hargis (1925) there has been an absolute and a relative increase of duodenal ulcer as compared with gastric ulcer which appears to have been confirmed by subsequent observations A ratio of 6 1 was found by Wilkie (1927), 8 1 by Young (1927) 6 1 by Albrecht (1930), in Germany 2 25 1 by Walton (1930) in London 9 1 by Lahey (1931), 6 1 by Balfour (1931) 4 1 by Moutier (1932), 5 6 1 by Emery and Monroe (1935), 12 1 by Eusterman and Balfour (1935), 7 3 by Allen (1937) 13 6 1 by Jennison (1938) 2 1 by Boyd (1942) 17 1 by Bockus (1943), 50 1 by Berk and Fredmann (1944) in Army personnel averaging 29 5 years 10 1 by Marshall and Gerber (1948) 9 5 1 for males and 4 4 1 for females by Jamieson, Smith and Scott (1949) and 7 3 1 by White (1951) According to Brooke (1950) *the relative incidence of duodenal to gastric* ulcer rose from 2 9 in 1940 to 4 7 in 1942 and then declined to 4 1 in 1946–47

It is of interest to note that clinically the incidence of duodenal ulcer is greatly in excess of gastric ulcer in the living subject but about equal in number at post mortem examinations

OCCUPATIONAL DISTRIBUTION

Friedenwald (1912) in 1 000 cases of ulcer of the stomach and duodenum, found that 31 were in cooks 18 in metal workers, 12 in porcelain workers 8 in miners 28 in tailors 15 in shoe makers and 19 in *blacksmiths* It is significant that doctors were found amongst the high incidence by Hurst and Stewart (1929) and amongst the low incidence by Ihre and Müller (1943) Duesberg (1938) found no incidence of ulcer in 622 monks as compared with 51 (0 74 per cent) amongst 6 923 foundry workers

Morris and Titmus (1944) found an incidence of 2 5 per cent in the leading professions wealthy independents directors and so on 14 per cent in employers managers lower professions 49 2 per cent in skilled workers, salesmen shop assistants and clerical workers 17 8 per cent in semi skilled workers and agricultural labourers and 16 5 per cent in unskilled workers

Sallstrom (1945b) believed that the frequency *in men depended on the* irregularity of their mode of living and affected particularly the building trade chauffeurs and drivers seamen artists musicians journalists and editors

According to Doll Jones and Buckatzsch (1951) social class did not *influence duodenal ulcer* incidence the *observed incidence of gastric ulcer* was two-thirds less than expected in professional and business executives and two-thirds more in unskilled and heavy manual labourers A high incidence of duodenal ulcer was found in foremen and business executives and a low incidence in agricultural labourers A significantly high incidence found in doctors was considered *to be due to a more refined standard of diagnosis* in this group Bus drivers and conductors showed no prevalent tendency to develop ulcer There was no evidence that irregularity of meals or shift work were of importance in the incidence of ulcer Anxiety and overwork was ✓

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complained of more frequently by men with proved duodenal ulcer, than by men with no dyspepsia In contrast, no association of ulcer with home worries was found

Doll (1952) found that in men gastric ulcer is between 2 and 5 times as prevalent in the poorest class as in the upper social classes (Registrar General's mortality figures) There was no difference for duodenal ulcer High incidence was thought to be characteristic of doctors (excess of diagnosis), executives, transport workers and fishermen, and low incidence to be characteristic of agricultural workers and clerks

SEX INCIDENCE

For *duodenal ulcers, diagnosed clinically*, the sex ratio of males to females was reported as follows Perry and Shaw (1893) 3 1, Brunner (1903) 9 1 Moynihan (1912) 4 1, Morley (1915) 21 1, Barford (1928) 4 3 1 Eusterman and Balfour (1935) 3 9 1, Jennison (1938) 3 7 1, Weidinger (1940) 3 1 1, McMullen (1941) 2 2 1, Bockus (1943) 4 2 1, Kiefer and McKell (1947) 4 7 1, and White (1951) 6 3 1

For *gastric ulcers* Brinton (1864) 1 2, Brunner (1903) 11 4 1, Moynihan (1912) 1 1, Morley (1913) 1 2 5, Mayo (1921) 3 6 1, Eusterman and Balfour (1935) 4 1, Weidinger (1940) 2 5 1, McMullen (1941) 1 6 1, Bockus (1943) 2 1 1, Smith and Jordan (1948) 2 2 1, White (1951) 1 1 1 Jamieson, Smith and Scott (1949) in a combined series of 3,258 patients found the sex ratio 3 5 for males to 1 female

In *autopsies for duodenal ulcer*, Musa (1922) found 1 1 in 47, Stewart (1929) 3 2 1, Portis and Jaffe (1938) 4 1 White (1951) 3 3 1 In *autopsies for gastric ulcer*, Stewart (1923) found 1 1, Portis and Jaffe (1938) 2 6 1, Gordon and Manning (1941) 2 1, and White (1951) 2 5 1

Sandweiss, Saltzstein and Farbman (1939) observed during the age period before sex activity rises the sex incidence of peptic ulcer to be equal between the sexes Nicol (1941) found that the sex incidence of peptic ulceration is remarkably constant throughout the world, being approximately 3 males to 1 female In hospital patients throughout Great Britain it varied from 1 to 1 in London and 8 to 1 in Scotland

AGE INCIDENCE

Doll, Jones and Buckatzsch (1951) calculated the incidence of peptic ulcer in London to be 5 8 per cent for men between the ages of 15 and 64 years and 1 9 per cent for women in the same age group Under the age of 55 years the male to female ratio was 4 5 1, over 55 years it was 1 4 1 The maximum incidence of gastric ulcer was in the decade 45–54 years, and of duodenal ulcers 10 years earlier In men the expectation of developing a duodenal ulcer was at a maximum and was constant between the ages of 20–64 years but the expectation of developing a gastric ulcer was greatest between the ages of 35 and 64 years

In a survey of 5 951 persons most of whom lived in London, they found that in men the incidence of peptic ulcer of all kinds rose to a maximum short of 10 per cent in the age-group 45–54 years, in women the highest incidence was 6 per cent and was not found until after the age of 55 years Before the age of 20 years there was none Doll (1951) stated that on the assumption that the age and sex incidence of the findings of Doll Avery Jones and Buckatzsch (1951) are applicable to the whole of England and Wales it can be calculated that 5 8 per cent of men and 1 9 per cent of women between the ages of 14 and 64 years suffer or have suffered, from peptic ulcer Similarly it can be estimated that 971,000 men and 478 000 women in England and Wales of all ages, have or have had ulcer The estimate of a total of 1,449,000 persons out of a population of 42 850 000 in 1946 compares with an estimate of 1,500 000 made by Avery Jones and Pollak (1945) on the basis of hospital experience and the national death rates for 1938

Incidence in the aged

Acute ulcer has no age limit although its occurrence is relatively rare in both the very young and the very old

Meyer and Saphir (1943) reported 16 patients with chronic ulcer, the youngest of whom was 60 and the oldest 83 years They emphasized that these ulcers were asymptomatic

Boles and Dunbar (1946), in an analysis of 4 000 consecutive autopsies found 97 (70 male and 27 female) cases of peptic ulcer in individuals over the age of 60 years 27 acute and 27 chronic gastric ulcers 18 acute and 23 chronic duodenal ulcers It is noteworthy that in only 10 (or slightly more than 10 per cent) was the clinical diagnosis made and that haemorrhage or perforation gave the clue to the diagnosis

Rafsky Weingarten and Krieger (1948) found that in 1,800 hospital admissions for peptic ulcer 22 2 per cent of the patients had attained the age of 60 years Kiefer and McKell (1947) found that in approximately 50 per cent of their series 152 patients were over the age of 65 years Mulsow (1949) in a review of recent American literature on peptic ulcer found an incidence of 19 2 per cent above the age of 60 years amongst 3,705 cases reported Levin Kirsner and Palmer (1949b) observed in 450 ulcer patients 41 over the age of 65 years—approximately 10 per cent there were 25 males and 16 females Twenty seven patients were between the ages of 65 and 69, 8 between 70 and 74, 6 between 75 and 79 and 1 was 82 years

Incidence in infants

The incidence of peptic ulcer in the newborn and the young infant is of considerable importance in the interpretation of their pathogenesis because the action of acid as a factor in the aetiology is completely eliminated

Cruveilhier (1829–35) reported multiple gastric ulcers in three infants aged one two and four weeks respectively The lesions occurring in the newborn are obviously acute ulcers or petechial erosions which result from sepsis general bacterial infections suppurative infection of the umbilical

cord, or thrombosis of the omphalo umbilical veins (Jacobi, 1909) Bolton (1913) refered to the case of Carteaux which vomited blood 20 hours after birth, Siebold's cases which perforated on the third day and a case described by Charcot in which two ulcers were found in the stomach of a 6½ months' foetus Berglund (1928–29) found 19 cases of acute ulcer in young children in a series of 1,323 autopsies performed in Stockholm Proctor (1925) reported on 8,260 cases of chronic peptic ulcer seen in the Mayo Clinic from 1906 to 1924, only two occurred in children

Kennedy (1933) pointed out that ulcer in the newborn as evidenced by melaena neonatorum is acute and typical of the lesion It is frequently multiple, may be in the stomach or duodenum, and either heals rapidly or else causes the death of the infant by haemorrhage or peritonitis Burdick (1940) described 10 cases of chronic duodenal ulcer in children aged 4½–13 years Eight of these were hospital cases, out of 21,231 admissions, and 2 cases were seen in private practice

According to Miller (1941–1942), who made observations on the gastric *acidity of 50 mature, breast fed infants,* during the first month of life, the relationship between the mother's gastric secretion and that of her infant at birth is emphasized by the fact that the percentage of mothers with achlorhydria *during pregnancy is identical with the number found in mature infants* at birth Miller observed achlorhydria in 6 of 50 infants, which is about the same ratio as that observed by Strauss and Castle (1932) in 3 of 20 mothers

According to Monrad (1941) (quoted by Priesel in Boller, 1954) no chronic gastric ulcers occur in infants Bird, Limper and Mayer (1941) have shown that ulcers in the newborn have special characteristics the great majority, of ulcers which are recognized, bleed seriously or perforate or both, in many the onset is precipitous without recognizable premonitory symptoms or signs, with few exceptions the lesions are acute, without cellular reaction or bacterial invasion Fraser (1943), commenting on the paper by Bird, Limper and Mayer (1941), considered it a remarkable finding that such a large number of cases occur in the newborn (38 in a total of 243 cases) Benner (1943) reported post mortem studies of 8 cases in about 500 routine autopsies on infants and children, all were of the acute type secondary to some other illness, generally severe infection

Ivy, Grossman and Bachrach (1950) considered that the occurrence of peptic ulcer in the newborn and the infant under the age of one year is exceedingly interesting from the viewpoint of pathogenesis because of the low acidity of the gastric content found in most instances White (1951) reviewed the autopsy and clinical material at the Children's Hospital in Boston for the last 25 years, in 1,437 autopsies there were 62 patients with gastric or duodenal ulceration In 32 patients the ulceration was classed as the Cushing-Rokitansky type secondary to or associated with diseases of the central nervous system such as tumours of the brain hydrocephalus encephalitis, mongolism, meningitis, and poliomyelitis Of the 30 patients without cerebrospinal diseases, 13 had duodenal and 17 had gastric ulceration, largely of "secondary type In the total autopsies there were also 83 cases of

oesophageal ulcer White (1951) concluded that in infants and children the type of ulceration and the conditions of diagnosis are quite different from those in adults but the incidence of gastro-duodenal ulcer seems low indeed compared with that of adults

It may be stated, in conclusion, that the ulcer which occurs in the new born and the young infant is an acute lesion secondary to the gross marasmic state which is invariably present in these patients

FAMILIAL INCIDENCE

Dreschfeld (1897) reported the presence of ulcer in 6 families Huber (1907) described 30 families in which 80 cases of ulcer occurred, 11 (15 per cent) of his cases had a family history Czernecki (1910) reported the history of a family in which a mother, a son and three daughters had a peptic ulcer Plaut (1913) found a long family history of ulcer in 22 per cent of 50 cases Dauwe (1913) reported 8 cases of ulcer who had a family history of the disease Spiegel (1918) in 121 ulcer patients found a family history in 26 4 per cent and only 5 5 per cent in 200 control cases Hurst (1921a) reported on 2 families in one the father and 2 out of 9 children were dyspeptic and 4 had typical symptoms in the other a mother, 3 sons and 1 grandson were affected Bauer and Aschner (1922) reported from a series of 205 cases of certified peptic ulcer and 400 controls that peptic ulcer is four times more common in the families of the ulcer patients than in those of the controls Aschner (1923) in 132 cases had 12 7 per cent with a family history whilst in 200 controls there was only 4 5 per cent. Ruhmann (1925) found a familial incidence in 48 per cent of 50 ulcer cases Wilkie (1927) believed that there was an undoubted hereditary tendency in ulcer particularly in females he reported two families in each of which three sisters had to be operated on for duodenal ulcer Riecker (1933) in 942 duodenal ulcer cases over a period of 5 years reported that 115 (13 per cent) had a family history of ulcer He believed that there can be no doubt that peptic ulcer is a familial disease

The author (Spira 1931) reported on a family living in adjoining houses as two separate households In the first household all the male members a man and his son, a stepson in law and his son had either a proved ulcer or symptoms suggesting ulcer, whilst in the second household composed of a stepson his wife and their son and daughter none complained of indigestion. The senior member of the first household who had a duodenal ulcer always complained that the food which was prepared by his Belgian wife was the cause of all their dyspepsias

The occurrence of peptic ulcer proved by x ray laparotomy or both in eight siblings of one family Americans of German Jewish descent (5 females aged 73 70 66 55 and 53 years and 3 males aged 62 61 and 58 years respectively) was reported by Plotz (1950)

It is obvious that this incidence cannot be advanced in support of the theory of the hereditary constitutional diathesis because it is far too high to be considered on the basis of a genetic law

Kimball (1951) considered that the reports of familial susceptibility do not of necessity prove the existence of an hereditary as contrasted with a congenital or even an environmental factor, but the author believes that in these cases, the environmental, that is, the food factor, is responsible

The inherited factor (the ulcer diathesis) as an element in the causation of ulcer and in the incidence in identical twins, has been examined in the Pathogenesis

SEASONAL INCIDENCE

Seasonal incidence with peaks in the spring and autumn have been reported, particularly by the older authors Smithies (1920) believed that the prevalence of epidemic infectious agents in the spring and autumn was responsible for the exacerbations at these times Hurst and Stewart (1929) blamed the vagaries of the weather for the seasonal variations of peptic ulcer incidence in England Mattison (1931) in a statistical examination of 1,342 cases found an incidence of 6–8 per cent for the months of January to August, but 10–12 per cent for the last four months of the year—a difference which is significant Rothe (1941) concluded from 7,488 observations for the years 1927–40 in Germany that there was a considerable seasonal periodicity with a maximum incidence in the winter but without marked peaks in the spring or autumn Eusterman and Balfour (1935) found a seasonal variation in 50 per cent of their cases and they suggested that possibly some nutritional factor was involved Sallstrom (1945d) found manifest seasonal variations with a minimum frequency during May—June and maximum frequency during August—September

GEOGRAPHICAL DISTRIBUTION

Brunner (1903) stated that there were 10 cases of peptic ulcer in England to 1 in Germany, and this was due to the English mode of life and the preponderance of meat in the diet

Rutimeyer (1906) reported the following geographical distribution in the incidence of peptic ulcer—Russia 0 8 per cent, Switzerland 2 6 per cent Austria 4 per cent, Germany 5 per cent, England 5 per cent, Denmark 16 7 per cent North America 1 3 per cent

According to Muller (1934) there is little occurrence of ulcer in the Argentine Mexico, West Indies and Panama

Ivy, Grossman and Bachrach (1950) concluded from a review of the literature that on the whole it appears that peptic ulcer has been noted less frequently at autopsy in the United States of America than in England, on the Continent or in Australia

RACE INCIDENCE

The white races living under primitive conditions appear to be less prone to ulcer

McCarrison (1912) performed 3 600 operations on primitive inhabitants of the Himalaya mountains but found no instance of peptic ulcer The racial difference in the Dutch East Indies was reported by Kouwenaar (1930) Post mortem examinations on 1 370 Chinamen in Sumatra showed that 11 per cent had ulcer or scars of 1,269 Javanese men only 0 63 per cent were affected of 399 Javanese women 1 per cent and of 123 Tamils 4 9 per cent The figures for the Chinese and Tamils correspond with those which he found in Europe Doll (1952) draws attention to the significance of the gross difference in incidence between closely associated communities which may furnish an important key to the fundamental causes of the condition [This subject is referred to in more detail in the chapter dealing with the Food Element in the Pathogenesis of Chronic Ulcer]

Gastric and duodenal ulcer is a relatively common disease in the coloured people in Abyssinia (Bergsma 1931)

Muller (1934) found the death rate from ulcer in the United States of America as follows for gastric ulcer in males—*whites* 3,345 or 1 in 197 2, and *blacks* 267 or 1 in 371 9 In females—*whites* 1 179 or 1 in 455 1 and *blacks* 233 or 1 in 389 7 For duodenal ulcer in males—*whites* 1 688 or 1 in 381 9 and *blacks* 79 or 1 in 1,256 9 In females—*whites* 398 or 1 in 1,349 5 and *blacks* 24 or 1 in 3,783 1

Boland (1935) found that during the ten year period 1925–34 among 60 000 patients admitted to the coloured division of the Grady Municipal Hospital Atlanta (a town of 300 000 inhabitants one third negroes) 119 cases were diagnosed as peptic ulcer, and during the same period among 75,000 patients admitted to the white division of the same hospital there were 295 cases of peptic ulcer He suggested (Boland 1942) that the increase in incidence in the black race in the Southern states of the United States of America is due to the abandonment of a native diet

Vassalo (1937) has never seen a case of peptic ulcer in a non European in Zanzibar Vint (1937) in 1 800 autopsies performed in Nairobi found 1 case of healed gastric ulcer none of duodenal ulcer and 3 cases of carcinoma of the stomach

Eagle and Gillman (1938) quoted Byers who in 1927 reported only 4 cases of peptic ulcer in 18 000 Bantu inmates during the years 1921–26 They analysed the incidence of peptic ulcer in 12 718 autopsies at the Government Mortuary and found the incidence was 5 in 3,373 Europeans (0 119 per cent) 8 in 8 328 Bantu (0 097 per cent) and 3 in 824 Eurafricans (0 364 per cent) 2 778 autopsies at the Johannesburg General Hospital gave 38 in 1,400 Europeans (2 714 per cent) 2 in 227 Eurafricans (0 881 per cent) and 5 in 1,144 Bantu (0 437 per cent) The combined statistics from these two institutions show that the European is apparently 7 times as susceptible to peptic ulcer as the Bantu and only twice as susceptible as the Eurafrican The authors draw attention to the imperfect information available in respect of diet race climate and environment in the aetiology of peptic ulcer

Gordon and Manning (1941) in 22 956 autopsies for the years 1920–37 found the following sex race incidence *acute gastric* ulcer whites 85 males

37 females, coloured people, 48 males, 31 females *Chronic gastric* ulcer whites, 63 males, 28 females, coloured people, 21 males, 7 females *Acute duodenal* ulcer whites, 86 males, 34 females, coloured people, 19 males, 18 females *Chronic duodenal* ulcer whites, 36 males, 6 females, coloured people, 6 males, 10 females The total represented, whites, 49 9 per cent males, 20 2 per cent females, coloured people 18 per cent males and 11 9 per cent females Ellis (1948–49) in a study of peptic ulcer in Nigeria reported a series of 123 cases of duodenal ulcer to 1 of gastric ulcer which suggested to him a different exciting cause for the two types of ulcer Most had pyloric obstruction Red and green peppers are ingested in very large quantities, rice being a part of the diet

CONCLUSIONS

It may be stated, in conclusion, that when the food element—with particular reference to the fat factor—is examined in relation to the incidence of peptic ulcer, a direct aetiological relationship will be established

The variation of this element is illustrated by the observation that until recent times the Negro in the United States of America has suffered less from ulcer than his white neighbour, but since his economical condition and his standard of living have improved, the tendency to ulcer has also increased

CHAPTER 22

DIAGNOSIS

The importance of a precise diagnosis as a preliminary to successful treatment needs no emphasis The physician should proceed with a planned examination of the patient in the following order (1) history taking (2) questionnaire, (3) physical examination and (4) laboratory investigations

HISTORY-TAKING (ANAMNESIS)

It is generally recognised that history taking must always be patiently carried out in suspected ulcer cases it should occupy the best part of the consultation the physical examination requiring relatively little time

After noting the family history and medical antecedents the patient should be allowed to tell his story in his own phraseology and in chronological order Having ascertained the characteristics of the patient s complaint particular attention should be directed to pain because it is the presenting symptom of the active peptic ulcer Detailed enquiry should be made as to its location if it occurs on the right side of the epigastrium it points to duodenal ulcer but if more centrally it points to gastric ulcer Enquiry should also be made as to the character of the pain that is its intensity extent mode of onset duration and 'rhythm (according to Moynihan there is a "triple rhythm food comfort pain for a gastric ulcer and a quadruple rhythm food comfort pain comfort for a duodenal ulcer) the nocturnal occurrence of the pain may also be of pathognomonic significance

QUESTIONNAIRE

The examiner should then proceed with a standard set of questions referring particularly to appetite nausea and vomiting bowel function sleep and loss of weight It is helpful to remember that appetite is usually diminished in all active pathological conditions and that the single exception to this rule is duodenal ulcer in which appetite is maintained or may even be excessive Loss of weight is unusual Constipation is almost invariably present Vomiting is an unusual symptom of ulcer when not associated with pyloric obstruction Nausea and heartburn (pyrosis) are paradoxically more often symptoms of hypochlorhydria than hyperchlorhydria *

* The author (Spira 1931) has described the lipstick sensation which may occur in susceptible people after eating a fatty meal The lips feel as if they were covered by a thin layer of fat such as would be produced by the use of a greasy lipstick It may be associated with a mild degree of salivation It is thought therefore that the lipstick sensation may represent a precursory stage of nausea

PHYSICAL EXAMINATION

When first seen the patient must always be subjected to a comprehensive physical examination This is facilitated by a standard routine which saves much time and avoids many pitfalls in the diagnosis

Only a very brief outline of the procedure will be indicated The examination consists of inspection, palpation, percussion and auscultation A record of temperature, pulse rate, blood pressure and urine examination may be made by a nurse before the general examination The heart and lungs should be examined before approaching the gastro intestinal system

Inspection

Inspection under bright illumination, preferably daylight, will draw attention at a glance to the physiognomy, the expression of the eyes and the appearance of the skin (its texture, discoloration, pallor, jaundice, naevi, pulsations, deformities, swellings, visible peristalsis) The appearance of the tongue should be noted, whether it is coated or clean, and whether glossitis is present

Palpation

Palpation will disclose enlarged organs (liver, pancreas, spleen, kidneys a mass of glands), succussion splash will draw attention to an enlarged gastric pouch Cutaneous hyperalgesia is an unreliable sign Deep pressure usually elicits a definite tenderness of the affected organ and epigastric tenderness is always present when the ulcer is active Radiographic examination will show that the point of maximum tenderness corresponds to the site of the lesion Muscular rigidity is not very common, but when present it is a sign of a large inflammatory reaction

Percussion and auscultation

Percussion and auscultation will help to distinguish between solid and hollow organs Surface markings are not very helpful because the shape, size and position of the stomach may vary considerably

The nervous system

The nervous system should be examined in order to exclude obvious organic disease

X-ray investigation

After an examination as outlined above, an x ray investigation is the first and most important step in the diagnosis and should be carried out by a competent radiologist It may be conclusive but is apt to misinterpretation if it is divorced from the clinical aspect of the disease Close co-operation of clinician and radiologist is therefore, essential

It may be helpful to draw attention to some specific points

The presence of a crater in the stomach (Haudek s niche) establishes the presence of an organic lesion the main distinction to be made is between benign and malignant ulcer

Although the question of malignancy of a duodenal lesion does not arise x rays of the duodenal cap do not always provide information with the necessary precision A persistent speck of barium caught in the mucosal folds with irregularities of the mucous membrane may be mistaken for an ulcer or a pseudo-diverticulum

Deformity of the duodenal cap without pain or tenderness on pressure is most likely to be due to a healed lesion. Fluoroscopy will disclose the shape position and behaviour of the stomach Alterations of function without permanent defect, such as spasm, irritability increased peristalsis and rapid peristalsis point unmistakably to the activity of a morbid process

Reflex spasm periduodenal adhesions, extrinsic irritations (particularly cholecystitis or chronic appendicitis) may lead to errors of diagnosis.

Gastroscopy

Gastroscopy is restricted by its limited field of vision but may be useful as contributory evidence of a gastric lesion the duodenal lesion is obviously out of the area which can be seen through the flexible gastroscope

The skill and temperament of the examiner greatly influence the value of the interpretation (Schindler, 1947) It is a valuable aid in diagnosing gastric lesions but only in connection with a well taken history physical examination radiographic study and laboratory data (Tesler 1947)

Gastroscopic examination is particularly useful in diagnosing mucosal atrophy erosions and early tumours Damage through suction may produce small submucosal and intramucosal haemorrhages which may be mistaken for pigment spots (Wolf and Wolff, 1943)

The risks of gastroscopy (Jones Doll Fletcher and Rodgers 1955) have been reported as 75 accidents with 32 deaths in a survey of 49 000 examina tions by 40 gastroscopists and a further 5 accidents with 3 deaths in an unknown number of gastroscopies

LABORATORY INVESTIGATIONS

The secretory function of the stomach is generally investigated by simple test meals Ewald s gruel meal being the most commonly used but many variations have been introduced (Boas, Riegel Fischer) Alcohol (Ehrmann) coffee (Katsch) and Liebig s extract have been suggested to replace Ewald s meal Rehfuss has introduced the fractional test meal but it should be realised that it only measures the concentration of acid The many limitations of the value of the fractional test meal have been pointed out (Moynihan 1919 Comfort and Osterberg 1931, Spira 1931 Hollander 1935 Hellebrand and Brogdon 1935–36 Eusterman and Balfour 1935) It may be recalled that the main objections are (1) the gastric tube acts as a foreign body in the stomach (2) the gastric tube may produce emotional inhibition (3) swal lowing of the saliva neutralises free hydrochloric acid (4) there may be violent duodenal regurgitation from retching and (5) there may be many day to-day variations in the response of a given subject

Gastric secretion after the administration of histamine is of value in determining the presence of free hydrochloric acid its absence may be accepted as strong evidence against a benign lesion

Bennett and Ryle's (1921) chart is somewhat misleading as it relates to 80 per cent of 100 normal students Rehfuss (1927), who studied groups of normal men with over 1,000 complete fractional analyses found that fully one third showed a tendency to high acid output and almost one third to a hyposecretory type He believed that the evacuation time was the real value of fractional test meals

It should also be remembered that there may be a high concentration of free hydrochloric acid in the presence of a malignant ulcer of the stomach just as there may be no free hydrochloric acid in the presence of a benign gastric ulcer, particularly in the aged, but both these occurrences are very rare

DIFFERENTIAL DIAGNOSIS

Many pathological conditions produce symptoms which are reflected in the digestive organs and may be specifically referred to the stomach, it is essential, therefore to sort out the gastric from the extra gastric pathology When the physician is satisfied that he is dealing with a disorder which is localised in the stomach, he should bear in mind that the first distinction which must be made is between benign ulcer and carcinoma It is helpful to remember that, broadly speaking, hyperchlorhydria and a white coated tongue are related to hypertrophic gastritis and are associated with ulcer, whilst hypochlorhydria and a red tongue (glossitis) are related to atrophic gastritis and are associated with carcinoma With ulcer there is a long history of intermittent periods of pain relieved by food and antacids a well maintained appetite and a tendency to constipation With carcinoma the history may be short and indefinite, the appetite is poor, with loss of weight, a tendency to diarrhoea, more constant pain which gradually gets worse and is not relieved by food It generally makes its first appearance in people over forty who have enjoyed good health and may follow soon after an acute infective illness which may be blamed for the fatigue and anaemia It may mimic ulcer and though the acid values are low, alkalies may give temporary relief

The conditions (excluding rarities) which must be considered in the differential diagnosis (organic reflex and systemic causes) may be classified as follows

Lesions of the Alimentary Canal

Intra gastric lesions

(a) Lesions of the oesophagus oesophagitis ulcer spasm hiatus hernia carcinoma
(b) Lesions of the stomach gastritis carcinoma diverticulosis
(c) Lesions of the duodenum primary and secondary duodenitis diverticulosis duodenal ileus (by pressure of mesenteric vessels)

Extra gastric lesions

(a) Lesions of the pancreas pancreatitis carcinoma
(b) Lesions of the liver sequelae of infections acute and chronic hepatitis cirrhosis
(c) Lesions of the gall bladder cholecystitis cholelithiasis
(d) Lesions of the intestine these are generally restricted to the colon constipation spastic and irritable colon inflammation of the vermiform appendix hookworm disease (in the tropics)

Lesions outside the Alimentary Canal

Diseases of pulmonary cardiovascular genito-urinary and central nervous systems

Functional disturbances

Fatigue tension psychosomatic and psychoneurotic disorders These should be diagnosed with extreme care and only after exclusion of all organic causes

CHAPTER 23

CRITIQUE OF ORTHODOX TREATMENT

Before describing the details of the author's treatment it may be useful to give a critical review of the orthodox methods

Orthodox treatment may be considered from two aspects (a) medical, and (b) surgical Both have in common the desire to abolish the acid factor, thus dealing with the effect rather than the cause of the disease

MEDICAL TREATMENT

The medical treatment approaches the problem from three angles rest, diet, and antacid medication

Rest

It is obvious that rest in bed will give the patient mental and physical relaxation which is beneficial in all forms of disease

Diet

Hippocrates (466–377 B C) and Celsus (30 B C–45 A D) introduced a reduced food intake for the treatment of the dyspepsias Cruveilhier (1829–35) suggested the administration of milk for the treatment of peptic ulcer in order to provide rest for the stomach Ziemssen (1871) added alkalis after Kussmaul (1869) had shown the presence of hyperchlorhydria by using the stomach tube and this method was further developed by Leube (1873) Ewald and Boas (1886) favoured a high fat diet, prescribing almond oil Cohnheim (1902) gave olive oil Lenhartz (1904) introduced gradually increased amounts of eggs in combination with iced milk Senator (1906) and Jarotski (1911) prescribed considerable quantities of iced butter, whilst Strauss (1911–12) and Petren (1913) prescribed large quantities of cream

Spriggs (1940) recommended cold fat bacon and ham and Barborka (1951) claimed that a diet relatively high in fat (cream, butter and olive oil) seems to be well tolerated

Modern dietetic treatment is now generally based on the Sippy (1915) method or one of its modifications, which consists in the administration of milk alternating hourly with alkalis Milk however has many intrinsic drawbacks it is not always tolerated and some patients are allergic to it It lacks vitamin B and may contain a toxic substance methyl glyoxal If

predigested by the addition of sodium citrate and sodium bicarbonate vitamin C is destroyed and infantile scurvy may occur Large quantities are required to provide the adequate amount of calories it is apt to produce flatulence and constipation and may lead to a full abdomen and obesity Side-effects of over feeding with milk have been shown in patients with hypertension and pulmonary tuberculosis and may lead to a sub-scurvy state (Archer and Graham 1936) The administration of large quantities of milk has been severely criticised by *Babkin (1944) and by Winkelstein Cornell* and Hollander (1945)

Good results have been claimed for hyperalimentation with amino-acid (protein hydrolysate) (Co Tui, Wright Mulholland Galvin, Barcham and Gerst 1948)

The continuous duodenal (Einhorn 1910) or gastric drip (Winkelstein 1932), according to these authors cures the ulcer but does not prevent its recurrence The choice of fluid for the drip appears to make little difference to the beneficial results (Winkelstein Cornell and Hollander, 1942) Jejunal feeding (Bockus 1924) has now been abandoned by its author (Bockus 1943) It should be noted that the effects of frequent feeding and the drip method can be ascribed to a great extent to the repeated initiation of isoperistalsis and consequent prevention of retroperistalsis

Antacid medication

Medicinal treatment is mainly concerned with control of the hydrochloric acid factor The following preparations have been used

The soluble antacids bicarbonate citrate and acetate of sodium and pot assium produce rapid neutralization but their action is not prolonged Intensive treatment may give rise to a delayed or rebound secretion of gastric juice and may produce toxic symptoms due to alkalosis (Hardt and Rivers 1923 Rafsky Schwartz and Kruger 1932 Kirsner and Palmer 1942) with renal changes and increased blood urea it may favour the formation of renal calculi (Eisele 1940) metastatic calcification and nephrocalcinosis *(Snapper, Bradley and Wilson 1954) and hypercalcaemia* with renal insufficiency secondary to excessive milk and alkali intake (Kessler 1955)

The insoluble antacids are only poorly absorbed and are therefore less likely to produce alkalosis They include bismuth salts calcium and magnesium compounds The aluminium compounds act on the hydrochloric acid solely as physical agents by absorbing the acid to the solid colloid Both the reactive and non reactive gels have a high constipating effect and faecal impaction may occur

Anion exchange resins are insoluble inert plastic substances capable of removing acid Effective neutralisers *in vitro* their *in vivo* effects have not been noteworthy and therapeutic results have proved unreliable The alkyl sul phates or detergents specifically counteract pepsin without significantly affecting gastric acidity

Antispasmodics belladonna and its alkaloids atropine hyoscyamine and

scopolamine depress the parasympathetic post ganglionic receptor substance, they are effective through their local anaesthetic action, but small doses may also have a marked effect on the secretions of the eyes, mouth and throat

Choline derivatives (Dibutolin) have an atropine like action

Autonomic blocking agents (Banthine tetraethylammonium chloride, hexa methonium) frequently give rise to side effects which may be distressing

Sympathomimetic drugs (amphetamine, Dexedrine) reduce motor function They are apt to produce restlessness, sleeplessness and loss of appetite, they may be useful in hypotensive patients

Sedatives (phenobarbitone and its sodium salt) appear to depress gastric secretion

Mucin has been suggested as a protective of the gastric mucous membrane It has a disagreeable taste and results are not encouraging

Protein hydrolysates, per os, have no specific value but may be useful in the elderly, under nourished patient Injected intravenously they frequently raise gastric secretion (Vanzant, 1932)

Amino acids (histidine, Larostidine) received surprisingly favourable reports when first introduced but these could not be confirmed by experimental or clinical research (Sandweiss 1936) Their use has now been abandoned in Great Britain

Histamine antagonists (histaminase, Torantil), have given disappointing clinical results (McHardy and Browne, 1943)

Antihistaminic compounds (Benadryl, Pyribenzamine, Neo-Antergan, The ophorin) do not inhibit gastric secretion and may even considerably increase gastric acid values (Doran, 1947)

Hormones do not appear to have produced any beneficial effects Cortisone and ACTH are definitely contra indicated The results of treatment with enterogastrone have been critically reviewed in Part I, Chapter 2, which deals with the secretory function Urogastrone and anthelone have not proved useful

Gastro intestinal extracts, powdered duodenal mucosa (dessicated and defatted), raw whole mammalian duodenum (Pepsac, Viodenum), and un specified protein free preparations of the stomach and small intestine (Robuden) are said to contain an "anti ulcer factor' resembling or identical with enterogastrone concentrates Hubacher (1946) claimed that of 54 pa tients treated with Robuden 44 showed good results without dietetic res trictions or confinement to bed Stolte (1950) compared under identical conditions the effect of Robuden and saline and also the effect of Robuden tablets and a placebo and found that the time for healing was exactly the same and that the symptoms disappeared in the same length of time

Vaccines and foreign protein injections appear to relieve pain but do not reduce gastric acidity (Vanzant and Snell, 1932), the mechanism of their action is not clear and their effect may be similar to placebos which are known to relieve pain

Berk (1951) summarises his comprehensive review of the drugs commonly used as follows It is obvious from the imposing number of drugs which have

been used in the treatment of uncomplicated gastro-duodenal ulcer that no specific pharmacological cure is presently available for this disorder All the drugs have inadequacies and many are handicapped further by undesirable side-effects He emphasized that the most striking feature of the medicinal treatment of *gastro-duodenal ulcer has been the overpowering concern with* gastric acidity , but that experience has demonstrated that effective clinical results may be obtained without the absolute and persistent neutralisation of gastric acidity sought by Sippy Indeed in many cases of simple un complicated gastro duodenal ulcer satisfactory clinical improvement may be secured without ever using antacids

Radiation therapy

X rays — Treatment by x rays which has as its object the production of hypo-acidity or anacidity has been shown in animals to produce late effects such as atrophy, proliferation metaplasia and fibrosis of the gastric mucous membrane (Warren and Whipple, 1923) This was confirmed by Betz (1947) who observed marked oedema of the submucosa as a pre ulcerative lesion and by Ricketts, Kirsner, Humphreys and Palmer (1948) who observed inflammatory changes and atrophy in man Brown, Scott Holman, Wood Finck Weiden and Davis (1952) suggested x ray irradiation to the stomach with local excision of the ulcer bearing portion of the duodenum and the gastric antrum (antroduodenectomy) followed by gastroduodenostomy, they claimed that the results after six months were encouraging

Radium —Jenkins and McGeorge (1942) and Ricketts Palmer Kirsner and Hamann (1948) used *radium* to produce a reduction of acidity Two 25 milligram or four 10-milligram needles placed in a stout rubber tube are swallowed by the patient and kept in the stomach for periods of 4–5 hours daily to give an exposure of 2,000–2,500 milligram hours

Douglas Ghent and Rowlands (1950 1951) who exposed stomachs of dogs to *beta* rays from an intra gastric balloon and produced atrophy of the gastric glands with an underlying normal submucosa and muscularis suggested the use of *beta* rays in the treatment of peptic ulcer

In view of the experimental evidence that radiation produces destructive lesions (*see* Chapter on Experimental Ulcer) it is somewhat paradoxical and it may be extremely dangerous to use a method which induces an irreversible atrophy to heal the ulcer

Results of orthodox treatment

Disappearance of the crater demonstrated by x ray examination as evidence of healing of the ulcer was reported by Flood (1951) out of 51 cases of gastric ulcer 19 healed in 4 weeks 24 in 8 weeks 5 in 12 weeks and 3 after 90 to 120 days In 145 gastric cases reported by Smith and Jordan (1948) the crater disappeared within 8 weeks in all except 9 cases

Incidence of recurrence

The incidence of recurrence after two years of medical treatment has been reported as 19 per cent in 392 patients (Jordan and Kiefer, 1932), 84 per cent in 1,435 patients (Emery and Monroe, 1935), 65 per cent in 225 patients (St John and Flood, 1939), 83 per cent in 151 patients (Raimondi and Collen, 1946), 20 1 per cent in 332 patients (Smith and Jordan, 1948), and 54 per cent in 233 patients (Flood, 1948) After a period of five years the reports are 46 per cent (Jordan and Kiefer, 1932), 93 per cent (Emery and Monroe, 1935), 50 per cent in 600 patients (Eusterman and Balfour, 1935), 78 per cent (St John and Flood, 1939), 46 8 per cent (Smith and Jordan, 1948), 78 per cent (Flood, 1948) The incidence of recurrence in gastric and duodenal ulcer does not differ to any great extent There is no evidence that the risk of recurrence under medical management decreases with the passage of time (Flood, 1951)

SURGICAL TREATMENT

It is now an accepted rule that medical treatment must be given an exhaustive trial in all ulcer cases before resorting to surgical intervention

Generally speaking, three types of operation, with many variations and modifications, are now in use (1) gastro enterostomy, (2) gastrectomy, and more recently (3) vagus (and sympathetic) section It should be emphasised that all these operations have only one common object in view, namely, the marked reduction or, if possible the complete abolition of the acid gastric secretions

Gastro-enterostomy

Gastro enterostomy was introduced in the treatment of duodenal as well as gastric ulcers on the assumption that by diverting food from the ulcerated area and by facilitating the massive regurgitation of alkaline juices into the stomach it would reduce gastric acidity and allow the ulcer to heal The fallacies of this conception were not immediately obvious

Cannon and Blake (1905) who examined the effects of gastro enterostomy, stated that intra abdominal pressure relations make gravity drainage impossible They observed that food goes through the patent pylorus rather than through the artificial stoma

Moynihan (1908) stated that gastro-enterostomy is most efficient only when gross mechanical obstruction exists a view also held by Quigley (1942)

Patterson (1914) extolled gastro-enterostomy because he considered it to be physiological and believed that it offered the surgical solution to a medically insoluble problem He argued that by directing the food away from the lesion and avoiding irritation of the ulcer, while at the same time allowing rapid drainage of the stomach and allowing a reflux of the alkaline intestinal juices into the stomach the ulcer would heal automatically

Truesdale (1915) showed that gastro enterostomy produced atrophy of the pyloric ring Horwitz Alvarez and Ascanio (1928) confirmed this observation

Types of gastro enterostomy

Many types of gastro enterostomy have been described They include anterior gastro-jejunostomy, posterior gastro-jejunostomy, gastro-jejunostomy with entero enterostomy, gastro-enterostomy with Roux en Y anastomosis, Devine s gastro-enterostomy with pyloric exclusion, and Finney s pyloroplasty (gastro-duodenostomy)

Mortality

The mortality rate of gastro-enterostomy varies from surgeon to surgeon Eiselsberg (1914) had 5 4 per cent in 284 cases, Haberer (1918), 1 2 per cent in 83 cases Paterson (1926), 0 8 per cent in 495 cases, Horsley (1930), 12 3 per cent in 57 cases, Moynihan (1932) 0 1 per cent in 1,000 cases More recently, Gardner and Hart (1948) had 7 3 per cent in 68 cases, and Walters Gray and Priestley (1948) 1 1 per cent in 88 cases

Lowering of gastric acidity

This was reported by the earlier observers (Kramer 1906 Katzenstein 1907) but more recent observers have reported very little reduction (Ender len, Freudenberg and Redwitz 1923 Lewisohn and Feldman 1925, Stein berg Brougher and Widgoff 1927 Lindsay and Evans 1929 Elman 1929 Hill, Henrich and Wilhelmj 1935, Walters 1936) While Page and Rankin (1937) and Snell (1937) claimed a reduction of acidity Engel (1937), Ochsner (1937) Maier and Grossman (1937) Holman and Sandusky (1938) Wangensteen Varco Hay, Walpole and Trach (1940), and Heuer (1944) could not confirm these results

Late results of gastro enterostomy

Improvement after gastro enterostomy was claimed by St John (1930) in 92 8 per cent of 119 cases by Balfour (1930) in 69 per cent of 500 cases of duodenal ulcer and 79 per cent of 100 cases of gastric ulcer Church and Hinton (1940) in 106 cases nearly all duodenal had 24 5 per cent cured and 29 2 per cent improved in 46 per cent there was no benefit and 16 per cent needed a further operation Heuer (1944) in 170 cases of duodenal ulcer showed satisfactory results in 73 per cent and in 31 cases of gastric ulcer 77 4 per cent In a collected series of 641 cases 71 per cent showed satisfactory results

Incidence of jejunal ulcer following gastro enterostomy

Various authors have reported the incidence of jejunal ulcer after gastro-enterostomy as shown in the Table

TABLE

RECORDED INCIDENCE OF JEJUNAL ULCER FOLLOWING GASTRO-ENTEROSTOMY

Author	*Year*	*Total No of cases*	*Reported incidence of ulcer (per cent)*
Eiselsberg	1914	230	3.0
Conybeare	1922	84	8.5
Pool & Dineen	1922	59	3.4
Lewisohn	1925	68	34.0
Paterson	1926	96	4.1 (with posterior gastro-enterostomy)
Paterson	1926	347	2.3 (with anterior gastro-enterostomy)
Carman	1926	4 146	5.3
Lewisohn & Ginsburg	1927	13 (gastric)	
		63 (duodenal)	34.0 (for 1915 to 1920)
Hurst & Stewart	1929	131	52.0
Luff	1929	744	28.0
St. John	1930	119	6.9
Gatewood	1930	154	6.0
Balfour	1930	500 (duodenal)	4.1
Balfour	1930	100 (gastric)	3.0
Benedict	1933	732	2.9
Haberer	1933	387	2.0
Walton	1934	2 154	1.4
Hinton & Church	1934	79	16.4
Emery & Johnson	1935	238	1.3
Wright	1935	1,730 (duodenal)	8.49
Wright	1935	507 (gastric)	10.45
Judd & Hoerner	1935	508	2.8 (for 1906—1911)
Judd & Hoerner	1935	4 383	2.8 (for 1912—1921)
Judd & Hoerner	1935	3 065	2.3 (for 1922—1926)
Judd & Hoerner	1935	2,382	1.9 (for 1927—1931)
Perman	1936	143	12.5
Judin	1937	426	5.0
Walters	1937	600	3.2
Newburger	1937	31	9.7
Moutier & Ghelew	1939	96	14.6
Fromme	1939	98	22.0
Church & Hinton	1940	106	46.2
Wangensteen & Lannin	1942	138	10.0
Heuer	1944	188	20.8
Linn	1946	1 027	30.6
Bruusgaard	1946	234	17.1
Cooper	1948	279	25.0

Walters Chance and Berkson (1955) emphasize that incidence of gastro-jejunal ulcer was low as first reported, but has gradually increased as the time of follow up has increased

The incidence of anastomotic ulcer after gastro-enterostomy is greater for duodenal than for gastric ulcer For duodenal ulcer it has been reported as 50 per cent within one year and 70 per cent within 2 years (Ivy, Grossman and Bachrach 1950)

Experimental evidence supports the clinical results Dott and Lim (1923) observed 90 per cent of jejunal ulcers in dogs after pyloric exclusion and gastro-jejunostomy, Montgomery (1923) found 4 large solitary ulcers in 60 dogs in which gastro-jejunostomy had been performed

Pribram (1923) referred to gastro-enterostomy as the gastro-enterostomy disease

Hurst (1928) thought that gastro-enterostomy was the commonest gastric disorder of the day and undoing gastro-enterostomy was the gastric operation he frequently recommended Eusterman and Balfour (1935) emphasized that jejunal ulcer may develop following gastro-enterostomy in patients who really never had an ulcer

Kalk (1936) considered that the duodenal reflex is of little importance in gastro-enterostomy since the duodenal secretions are practically neutral the operation is followed either by the establishment of an atrophic gastritis when the patient improves, or by a superacid gastritis when the patient develops a jejunal ulcer or a recurrence

Lannin (1945) wondered how many lives had been lost by inflicting upon patients such disastrous operations as those suggested by Eiselsberg (1895) Schmilinsky (1918) and Devine (1925) which do not require experimental evidence to bring to light the dismal record of these operations Gray and Lofgren (1948) observed 825 patients who had a gastro-enterostomy stoma taken down and a partial gastrectomy performed for jejunal ulcer mal functioning stoma gastric ulcer and gastric carcinoma

Microcytic anaemia following gastro-enterostomy was reported by Larsen (1934) Hartfall (1934) Lublin (1936) and Bruusgaard (1946)

Post-cibal or dumping syndrome after gastro-enterostomy was reported by Hurst (1913) Mix (1922), and Evensen (1942)

With the exception of a few surgeons the operation of gastro-enterostomy has now been generally abandoned the only indication for it is pyloric obstruction when the patient is not fit for more drastic surgery

Gastrectomy

Gastrectomy was introduced as the operation of choice when it was re cognised that gastro-enterostomy had failed to achieve its object

Types of operation

A considerable number of gastrectomies have been described but funda mentally most of them are modifications of the Billroth I (1881) and Billroth II (1885) types of operation Vitkin (1940) believed the formation of a

sphincter in the anastomotic region after gastrectomy of the Billroth II method to be quite impossible He explained that the periodic closing and opening of the anastomosis is caused by peristaltic contractions and distensions of the efferent intestinal loop nearest to the anastomosis

According to Finsterer (1926), the extent of the resection and not the removal of the pylorus decides the result, for Mage (1942) the basic prerequisites of subtotal gastrectomy are removal of the pylorus, a radical resection of all antral tissue and the excision of the ulcer Apart from various technical modifications of the operation more and more extensive resections were advocated till hardly any gastric remnant was left (Visick, 1948) ignoring the fact that small stomachs may give rise to oesophageal regurgitation Wangensteen (1952) advocated a segmental resection constituting not more than 10 per cent of the stomach or 15 per cent of the acid bearing area, whilst Deloyers (1955) suggested the removal of the whole acid bearing area in order to produce an absolute anacidity (inverted gastrectomy) Rutter (1953) reported a case of ischaemic necrosis of the stomach, which was due to over enthusiastic devascularisation of the proximal part of the stomach

Mortality rate

Ivy, Grossman and Bachrach (1950), in a collected series, reported an average mortality of 6 4 per cent (0–29 9 per cent) in 850 patients with gastric ulcer and 2 8 per cent (1 3 to 5 4 per cent) in 3,710 patients with duodenal ulcer

Reduction of acidity

Immediate reduction of gastric acidity after gastrectomy was observed by Crohn (1925), Lewisohn and Feldman (1925), Portis and Portis (1926), Klein (1927, 1935), Lewishon and Ginzburg (1927), Steinberg, Brougher and Vidgoff (1927), Morley and Roberts (1928–29), Winkelstein (1929), Comfort and Osterberg (1931), Priestley and Mann (1932), Walters (1936), Wilhelmj, McCarthy and Hill (1936), Hill O Brien and Wilhelmj (1937), St John, Flood and Gius (1939), Wangensteen, Varco, Hay, Walpole and Trach (1940), and by Connell (1931, 1934) after fundusectomy

A reduction of acidity in proportion to the extent of the resection was observed by Finsterer (1926), Holman and McSwain (1943), Heuer and Holman (1943), Heuer (1944), Gaviser (1948), Cross, Ferguson and Wangensteen (1951)

According to Wangensteen and his colleagues (1940) extensive gastric resection *per se* does not produce achlorhydria, extensive gastric resection combined with gastro jejunostomy will usually produce achlorhydria, excision of the pylorus and antrum fails to produce achlorhydria

A tendency to a gradual return of gastric acidity after partial gastrectomy was observed in dogs by Fauley, Strauss and Ivy (1932) They observed that resection of at least 66 per cent of the stomach in 10 out of 12 dogs resulted in varying degrees of compensatory hypertrophy of the gastric remnant The jejunum at the stoma was also hypertrophied The emptying time of the

stomach was permanently decreased in spite of the hypertrophy The acidity of the gastric content returned practically to normal in from three to five months Jejunal ulcers developed in 3 of the 12 dogs

Priestley and Mann (1932) suggested that the more rapid emptying time of the stomach which usually occurs after partial gastrectomy is a factor in producing the lower acidity Strauss Strauss Levitsky, Scheman Siedmon, Arens Meyer and Necheles (1937–38) found that slower emptying time offers better clinical end results than rapid emptying time

According to Oliver (1949) no ulcer will develop if the whole stomach has been removed whereas a subtotal gastrectomy leaving 25 per cent of the stomach, will result in a high incidence of stomal ulcer Oliver (1951) concluded from his experiments on Mann Williamson dogs that bilateral supra diaphragmatic resection of the vagi plus extirpation of the pyloric antrum will adequately suppress a gastric secretory response and result in the necessary degree of anacidity to prevent the development of stomal ulcer According to Ivy, Grossman and Bachrach (1950) dogs after subtotal gastric resection show a gradual return to gastric acidity rather than a tendency for achlorhydria to occur with time The gastric phase of gastric secretion decreases by 30 to 40 per cent

Late results of gastric resection

Walters Lewis and Lemon (1940) in 197 patients had excellent results in 83 5 per cent after the Polya type operation without undue diet restrictions while Watson (1947) found that after the Polya operation in 132 patients the results were excellent in 39 (43 3 per cent) of 90 followed up for under 3 years and 14 (33 3 per cent) of 42 followed up for over 3 years

Ivy Grossman and Bachrach (1950) reported the satisfactory late results of gastric resection in 1 487 collected cases of duodenal ulcer as 92 7 per cent (81 6–98 2) and 499 cases of gastric ulcer as 95 9 per cent (90 to 100), Rauch (1952) in 893 resections reported 26 6 per cent excellent 63 per cent satisfactory and 10 4 per cent poor results

Wallensten and Gothman (1953) reported a mortality of 4 9 per cent with a recurrence in 1 1 per cent, and the dumping syndrome in 10 1 per cent in 103 gastric ulcers and a mortality of 1 2 per cent with a recurrence of 3 7 per cent in 261 duodenal ulcers MacLean Hamilton and Murphy (1953) found that when they resected all but 10 to 15 per cent of the acid secreting area (segmental gastric resection) accompanied by pyloroplasty the food intolerance was limited to milk ice and cream McDonald Gillespie and La Bree (1953) obtained 92 per cent excellent results in 122 patients after a 75 per cent resection of the Hofmeister short loop type Harvey St John and Volk (1953) in an analysis of their failures after partial gastrectomy comparing their results for the periods 1936–45 and 1946–51 found that the satisfactory results were 85 and 75 per cent respectively

Cross Ferguson and Wangensteen (1951) claimed that an extensive gastric resection in which 74 per cent of the acid secreting portion of the stomach by weight is excised leaving 10 per cent of the entire stomach as

the upper fundic pouch anastomozed to the antrum, will protect against the histamine in-beeswax provoked ulcer in dogs A segmental resection in which 25 per cent of the stomach by weight is left as the fundic pouch will not protect against an ulcer provoked by histamine in beeswax, whether or not a complemental vagotomy is done

Kirschner (1929) believed that the administration of food immediately after resection would break down the initial barrier which delayed the return of normal function

Complications of gastrectomy

Microcytic anaemia — Microcytic anaemia following gastrectomy was reported by Berg (1930), Ivy, Morgan and Farrel (1931), Bockus, Bank and Willard (1932), Boyd (1938) in dogs, Bussabarger and Jung (1936) in rats Goldhamer (1934), Bussabarger and Ivy (1936), Bussabarger, Ivy, Wigodsky and Gunn (1939) in monkeys, Morley and Roberts (1928), Gordon Taylor, Hudson, Dodds, Warner and Whitby (1928–29), Hartfall (1934), Larsen (1934), Still (1936), Munakata (1939), Bruusgaard (1946), Watson (1947), Smith and Jordan (1948), Gaviser (1948), Muir (1949), Wells and Welbourn (1951) in the human According to Farris, Ranson and Collier (1943) gastrectomy *interferes with the metabolism of iron*

Macrocytic anaemia — Macrocytic anaemia was reported after extensive gastrectomy by Moynihan (1911), Rowlands and Simpson (1932), Vaughan (1932), Hurst (1932), Rhodes and Grunberg (1942)

Callender, Turnbull and Wakisaka (1954) found that after total gastrectomy the secretion of the intrinsic factor is greatly reduced, the reduction being of the same degree as occurs in addisonian pernicious anaemia

Gastro jejunitis — Konjetzny (1935) reported on gastro-jejunitis referring to its local and systemic consequences as the most important reason for the failure of operations on the stomach particularly the bacterial infection of the gastric remnant which follows surgical intervention

Fat absorption — After subtotal gastrectomy fat absorption is impaired, between 20 and 40 per cent of the dietary fat is lost as compared with less than 10 per cent in healthy persons (Rekers, Abels and Rhoads, *1943*)

Gastrectomy and pulmonary tuberculosis — Olmer (1947) established a relationship between gastrectomy and pulmonary tuberculosis Jones, Culver Drummey and Ryan (1948) observed loss of weight in spite of apparently adequate food intake

Vitamin B deficiencies — According to Welbourn Hughes and Wells (1951) vitamin B deficiencies *are* relatively common after gastric operations and have been found in 10 per cent of subtotal gastrectomies one or more years after operation Hyporiboflavinosis and incipient peripheral neuritis due to aneurine deficiency, are the commonest syndromes Less common conditions are established peripheral neuritis Wernicke's encephalopathy and other disturbances of consciousness and pellagra

Clostridium welchii — Howie, Duncan and Mackie (1953) found in 12 of 15 patients examined during the first week *after the operation numerous*

Clostridium welchii in films and cultures from the stomach contents and in 8 of the 15 patients small amounts of welchii and toxin were also demonstrated

Necrotising enteritis —Williams and Pullan (1953) described in 10 patients a necrotising enteritis following gastric surgery Of the patients 5 died, and necropsy showed that in all of them the mucosa of the small intestine had sloughed over a considerable area—the aetiology is unknown

Other complications — Disturbances of the gall bladder biliary stasis and gallstone formation were observed by Jankelson and Robins (1943) and Majoor and Suren (1947)

Browne and McHardy (1944) listed the following medical problems after operation recurrent or anastomotic ulceration, haemorrhage from ulceration or gastritis, oedematous stomal obstruction resulting from ulceration hypoproteinaemia or gastro-jejunitis, haematopoietic disturbances anaemia motor and secretory dysfunction (reservoir loss trituration abnormality digestive deficiency gastrogenic diarrhoea) deficient absorption particularly of iron and calcium manifestations of vitamin deficiencies particularly glossitis, chronic jejunitis, chronic gastritis

Boller (1954) divides the pathological consequences following gastrectomy into two groups

(1) Those which show no pathological substratum and include the small stomach, deficiency of acid secretion cascade emptying gastric and intestinal flatulence filling of the afferent loop the so-called dumping syndrome delayed hypoglycaemia metabolic disturbances aerophagia (2) Those which have a pathological substratum and include gastritis of the gastric remnant anastomositis operative artefacts anastomotic and jejunal ulcers jejuno-colic fistula carcinoma of the remnant Disturbances of the liver gall-bladder and pancreas and intestinal function are not infrequent complications

Metabolic syndromes are responsible for the marked fatigue and asthenia which are often present.

Haemorrhage following gastrectomy

Post-operative haemorrhage varies considerably Walters (1941) reported 11 6 per cent in 112 cases Church and Hinton (1942) 4 5 per cent in 44 cases Wilkinson and Tracey (1946) 24 per cent in 41 cases Holman (1948) 3 8 per cent in 53 cases Morey and Plummer (1955) 7 9 per cent in 74 cases

Ivy, Grossman and Bachrach (1950) reported that in a collected survey (Ivy and Fainer) of 1,593 patients, 555 or 3 48 per cent with anastomotic ulcer had manifest haemorrhage at some time in the course of their disease

There seems to be some relation of post-operative haemorrhage to pre-operative haemorrhage For patients who bled pre-operatively 4 out of 37 (10·8 per cent) bled post-operatively (Eliason and Johnson 1936) 7 out of 15 (46 6 per cent) (Church and Hinton 1940) 12 out of 76 (15 8 per cent) (Cooper, 1948) For patients who did not bleed pre-operatively the same authors show respectively 2 out of 114 (1 8 per cent) 15 out of 91 (16 5 per cent) and 16 out of 214 (7 4 per cent)

the upper fundic pouch anastomozed to the antrum, will protect against the histamine in beeswax provoked ulcer in dogs A segmental resection in which 25 per cent of the stomach by weight is left as the fundic pouch will not protect against an ulcer provoked by histamine in beeswax, whether or not a complemental vagotomy is done

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The ' dumping syndrome

Symptoms — The post gastrectomy symptoms usually referred to as the dumping syndrome are warmth sweating weakness palpitation fullness tightness and pain in the epigastrium nausea and sometimes vomiting which relieves the symptoms They are brought on by a meal either immediately or after a delay of one or two hours They appear to be produced by sympathetic stimulation

Symptoms were attributed to *hypoglycaemia* by Glaessner (1940), Evensen (1942), Gilbert and Dunlop (1947) Barnes (1947) Lawrence (1947) Zollinger and Hoerr (1947) Debray, Pergola and Muffang (1950), Warter Rouillard and Morin (1951) and to *jejunal distension* by Berkman and Heck (1945) Irvine (1948) Machella (1949), Butler and Capper (1951) Pontes and Neves (1953)

Adlersberg and Hammerschlag (1947) made a distinction between early and late symptoms distension being responsible for the early and hypoglycaemia for the late symptoms Schechter and Necheles (1949) ruled out hyperglycaemia Custer, Butt and Waugh (1946) produced relief of symptoms by the administration of hydrochloric acid Hosford (1949) observed a feeling of fullness with both slow and rapid emptying Smith (1951) attributed it to lack of potassium brought about by the release of some adrenaline substance in the blood and unduly rapid absorption of ingested carbohydrates Wells and Welbourn (1951) blamed rapid emptying stasis and reflux reduction of acid and removal of the intrinsic factor Smith, Fraser Staynes and Willcox (1953) attributed it to precipitate emptying Muir (1949) and Schofield and Anderson (1953) to afferent loop stasis

Incidence — The incidence of the dumping syndrome was reported as 12–15 per cent by Jordan (1942), 14 per cent by Mateer (1942), 10 per cent by Ingelfinger (1944), 5 6 per cent by Custer, Butt and Waugh (1946), 37 7 per cent by Gilbert and Dunlop (1947), 5 25 per cent by Zollinger and Hoerr (1947) 3 per cent by Lake (1948), 8 6 per cent by Jordan (1948) 6 3 per cent by Adlersberg and Hammerschlag (1949) 75 per cent by Muir (1949–50) 11 9 per cent by Butler and Capper (1951) 10 per cent by Wallensten and Gothman (1953) 41 3 per cent by Meurling (1954), 13 5 per cent by Morey and Plummer (1955)

Jordan (1941) found that symptoms lasted more than 4 years in 50 per cent of her cases Custer Butt and Waugh (1946) believed that they lasted indefinitely

Vagotomy

Vagotomy was introduced by Dragstedt and Owens (1943) as a physiological solution of the ulcer problem They revived and enlarged the less extensive operation of Pieri and Tanferna (1932) They based their operation on Hartzell s (1929) experiments on dogs which suggested a neurogenic origin for the excessive gastric secretions but ignored Vanzant (1931) who reported that two years later the gastric secretions of Hartzell s dogs had

The following table gives the reported incidence of gastro jejunal ulcer after gastrectomy over a number of years

TABLE

INCIDENCE OF GASTRO JEJUNAL ULCER FOLLOWING PARTIAL OR SUBTOTAL GASTRECTOMY

Author	*Year*	*Total No of cases*	*Reported recurrence (per cent)*
St John	1930	76 (partial gast e tomy)	3 6 (marginal ulcer)
Starlinger	1930	13 000 (in a summary of rese t on)	0 9 (after B llroth I m thod)
Starlinger	1930		0 6 (after Billroth II method)
Wright	1935	109 (coll cti enq ry)	2 8
Perman	1936	76	1 3
Moutier & Ghelew	1939	33	27 2 (recurrence) 46 5 (gastritis)
McClure & Fallis	*1940*	74	4 0 (ecu) 4 0 (suspe ted r currence)
Walters Lewis & Lemon	1940	1 212	2 5
Mage	1942	502	8 0
Kiefer	1942	143	11 2
Bartels & Dulin	1942	92	4 3
Sanders	1945	101	8 0
Rienhoff	1945	255	9 0
Wilkinson	1946	173	6 8
Allen & Welch	1946	129	2 3
Watson	1947	68	4 4
Lake	1948	600	1 0
Gaviser	1948	231	1 7
Visick	1948	93	3 2
Gardner & Hart	1948	100	5 0
Steinberg	1948	319	0 6
St John et al	1948	373	1 4
Rauch	1952	893	1 5
Wallensten & Göthman	1953	91 (gast ic)	0 9 (afte B llroth I operat n)
Wallensten & Göthman	1953	239 (duodenal)	3 7 (after Billroth I operation)
Wallensten	1954	203	8 4 (after Billroth I operat)
Wallensten	1954	322	2 5 (after Billroth II ope u)
Morey & Plummer	1955	74	8 1

produced a stimulating effect by abolishing the cephalic phase of secretion by severing the vagus nerves to the main stomach of both Pavlov and Heidenhain pouch dogs Gastro enterostomy effectively prevented the stimulating effect of vagotomy on the gastric phase of secretion They suggested that an acid environment produces an inhibitory effect on antrum function

Effect of vagotomy on gastric secretion and motility

It is generally agreed that vagotomy produces an immediate reduction of both gastric secretion and motility (*See also* Physiological Considerations)

Vanzant (1931–32) has pointed out that although numerous observations have been made on the effect on the stomach of section of the vagus nerves they have been made only for short periods after operation

Meek and Herrin (1934) found that the lengthening of the emptying time of the stomach after thoracic vagotomy varied with the consistency of the food the emptying time being delayed after solid food but remaining at the normal figure after liquid food They concluded that the evidence points to the vagus as a nerve necessary for the existence of normal gastric tonus and that emptying depends in some way on the degree of this tonus

Permanent anacidity was claimed by Winkelstein and Berg (1938), no return after one year by Paulson and Gladsden (1949) and Postlethwait, Bradshaw, McRea Williams and Deaton (1950), and after 28–41 months by Palumbo Marquis and Smith (1951)

A return to normal acidity tends to occur after a relatively short space of time (Moore, Chapman, Schulz and Jones, 1947, Vanzant, 1947, Ruffin and White, 1948 Shay Komarov and Gruenstein 1949, Paulson and Gladsden 1949) It would appear that the stomach is so nearly autonomous that its secretory functions will return almost to normal some time after bilateral vagotomy if not, the patient requires parasympathomimetic drugs to counteract the gastric atony (Stein Steigman and Meyer 1947)

Night secretion is greatly reduced in volume (Clarke Storer and Dragstedt 1947, Hansen 1948 Stein and Meyer 1948)

Effect of vagotomy on visceral function

Vagotomy not only interferes with the secretion of the stomach but also with the secretion of the pancreas (Baxter 1931) Vaso-dilatation may be responsible for this effect (Greengaard Grossman Roback and Ivy, 1944) It interferes seriously with a number of essential visceral functions, and from the physiological standpoint it must be regarded as a grave operation (Komarov 1942 Walters Neibling Bradley, Small and Wilson, 1947, Moore 1947 Govaerts and van Geertruyden 1949) Boles (1948) thought that it may have been too soon to form conclusions but not too soon to voice a protest concerning what had the appearance of becoming a mass experiment on human beings that is fraught with potentially serious and permanent disabilities

returned to normal Vanzant (1931) confirmed Pieri, Lapenna and Tanferna's observations that the changes brought about by the destruction of the vagus nerves which resulted in marked reduction in the capacity of the stomach to secrete acid were not permanent in the human subject and her studies confirmed that this was also true in the dog

Effect of vagotomy on the experimental animal

Auer (1909–10) has pointed out that the various operations on the extrinsic nervous system considerably reduce the general body resistance A rough diet which has no effect on the intact stomach produces ulcerations after bilateral vagotomy (Beazell and Ivy, 1936)

After vagotomy the period of survival in Mann-Williamson dogs is shortened (Saltzstein, Sandweiss, Hammer, Hill and Vandenberg, 1947), the occurrence of ulcer which is not prevented (Beaver and Mann, 1931, Oliver, 1947), may be produced experimentally (Greggio, 1916) and results in death in rats (Shay, Komarov and Gruenstein, 1948) It prevents ulcer in the Shay rat in the time limit of 24 hours (Harkins and Hooker, 1947) It does not prevent the cinchophen produced ulcer (Hilsabeck and Hill, 1947)

Lillehei, Lewis and Wangensteen (1950) found that vagotomy gives virtually complete protection against histamine provoked ulcer in dogs in good health but not in dogs in bad health Their studies of gastric motility after vagotomy alone and vagotomy with various drainage procedures demonstrated that ulcer incidence increased as the time for gastric emptying decreased, and that a procedure which promotes gastric drainage after vagotomy leads to a higher incidence of stomal ulceration

Effect of vagotomy on the gastric mucous membrane

Vanzant (1947) showed in dogs that excessive secretion of mucus was one of the most striking and typical results of vagotomy Deleterious effects on the gastric mucous membrane, loss of lustre, dullness and reddening was observed by Wolff (1948) atony of the muscularis mucosae and decreased number and size of gastric rugae were reported by Palmer (1949)

Glass, Mersheimer and Svigals (1951) observed, after subtotal gastrectomy and successful bilateral vagotomy an increase of the muco-proteose fraction of mucin and complete depression of the muco protein They concluded, therefore that the degradation of the mucous coating of the stomach after vagotomy cannot be considered a favourable feature which might contribute to a better protection of the gastric mucosa from trauma or peptic digestion

Necheles and Jefferson (1952) found in dogs that while bilateral vagotomy led to dilatation of the stomach and constant vomiting the additional section of the left phrenic nerve produced rapid emptying of the stomach and no vomiting occurred Additional section also overcame cardiospasm which often followed bilateral vagotomy

Evans, Zubiran McCarthy Ragens Woodward and Dragstedt (1953)

may reach an alarming degree (Boles 1948) Some patients continue to complain of weakness nervousness and indigestion even though they have been relieved of pain and other symptoms attributable to their ulcer (Ruffin and White 1948) Usual complications are (a) gastric retention due to atony and dilatation, (b) diarrhoea, which is not consistently related to achlorhydria or relieved by the administration of acid, although it appears to benefit by the administration of pancreatic extracts and (c) spasm of the lower third of the oesophagus

The results are inconstant variable and in most cases unpredictable There may be recurrence, failure to heal and unsuspected perforation may develop (Walters Neibling Small and Wilson 1947) If the human stomach resembles that of the rabbit then gastric ulcers may occur if rough food is eaten (Ivy, 1946, Moore 1947)

Chamberlin and Winship (1947) question the routine use of the abdominal approach, particularly for the occasional performer of vagotomies

Recurrence of gastric ulcer after complete vagotomy

Recurrence after vagotomy has been reported in 15 patients by Warren (1947), in 5 of 74 by Moore (1947), in 6 of 52 by Hansen (1948) and 1 of 50 by Collins and Stevenson (1948) Rob (1948) described a recurrent ulcer 6 months after an adequate vagal section Dragstedt, Camp and Fritz (1949) reported in a series of 197 patients, that 2 gastric ulcers developed after complete vagotomy although nocturnal hyperacidity was abolished Daniels (1950) reported perforation of a duodenal ulcer 15 months after vagotomy Weber Goldblum and Gregg (1950) reported 3 cases of recurrent ulcer, in 2 of the cases after vagotomy for duodenal ulcer gastric ulcers were observed which had occurred subsequently to the operation Morrissey (1950) in 79 cases of duodenal ulcer, reported the development of two cases of gastric ulcer 6 months after successful vagal section

Pollock (1952) found from his collected cases that of 736 patients with peptic ulceration *treated by vagotomy alone* 73 who had been treated for gastric ulcer had a proved recurrence rate of 18 per cent, 74 patients treated for jejunal ulcer had a proved recurrence rate of 16 per cent of 589 patients with duodenal ulcer the recurrence rate was 6 per cent Many more patients had symptoms suggesting recurrent ulceration but the recurrences were not proved

Hand and Patey (1953) in a follow up of 72 cases of duodenal and jejunal ulcer treated by vagotomy from 1946 to 1950 found that gastric ulcer is a complication of vagotomy for duodenal ulcer (3 out of 12 cases) Recurrence of the duodenal ulcer occurred in 5 out of 12 cases of simple vagotomy and in 4 out of 28 cases of vagotomy plus pyloro-duodenectomy and in 1 out of 8 cases of vagotomy plus gastro-enterostomy They concluded that the only group of cases in which vagotomy has an established position as a routine procedure is that of gastrojejunal ulcer after subtotal gastrectomy

Wells (1954) in a follow up of 39 cases of proved anastomotic ulceration treated by vagotomy, found that in 25 of the gastrectomies only two-thirds

Effect of vagotomy on pain

Complete division of the vagus nerves in cases of ulcer produces complete and permanent relief of distress but the sensation of hunger is not abolished by complete vagotomy, inflation of a balloon in the stomach produces a feeling of distension or actual pain (Dragstedt, Woodward, Harper, and Storer, (1948)

Extent of section

Schilling, Feldmann and Scott (1948) after an extensive review concluded that it is now conceded that unless vagotomy is complete, its effects on the gastro intestinal tract are either absent or variable

Krehl (1892) pointed out that it is most remarkable that a minute branch of the vagus can so perfectly take over all the functions of the two big nerves (Alvarez, 1948)

Total vagotomy may be difficult to achieve because of the considerable variation in the number of main trunks and accessory branches of the vagus nerves which have been described (Bradley, Small, Wilson and Walters 1947, Miller and Davis, 1947, Chamberlin and Winship, 1947, Doubilet and Shafiroff, 1948, Shapiro and Robillard, 1950)

Choice of operation

According to Thorek (1947) the *transthoracic approach* has the following advantages (1) good exposure and (2) more complete sectioning of the nerves Its disadvantages are (1) the lesion cannot be examined (possible malignancy), (2) pyloric obstruction cannot be corrected, (3) post vagotomy gastric atony cannot be corrected (4) post operative pain in the incision and costovertebral joint may result, and (5) gastro enterostomy is a difficult and unsatisfactory procedure when performed as a secondary operation on a dilated and atonic stomach It is, therefore generally accepted that the *transabdominal route* is to be preferred because it allows a proper view of the affected organ and allows for additional surgery should this be required

Operative risks

Weeks, Ryan and Van Hoy (1946) reported 2 deaths associated with supra diaphragmatic vagotomy Thorek (1947) recorded 3 deaths after 25 vagotomies in 18 months, none of which, however, could be directly attributed to the operative procedure Orr and Johnson (1948) claimed no deaths in 115 cases Hoerr Brown Rumsey and Crile (1952) reported an operative mortality in sub diaphragmatic vagus section plus gastro enterostomy of 1 out of 147 patients

Favourable results which have been claimed include immediate relief of pain reduction of acidity, healing of the ulcer and a paucity of recurrence

Unfavourable results, frequently reported, are diminished or absent motility of the stomach dilatation and retention epigastric fullness nausea, vomiting and diarrhoea The dilatation and retention resulting from diminished motility

conclusion that there is little place for vagotomy alone in the treatment of duodenal ulcer and that it should not be performed for gastric ulceration because of the high incidence of unsuspected malignant disease and because the post-operative results compare unfavourably with gastric resection Pollock (1952), from a review of the collected results of vagotomy in 1,524 patients with peptic ulcer (1,314 duodenal, 127 gastric, 82 jejunal and 1 oesophageal), concluded that vagotomy alone is an unsatisfactory operation but it yields better results when combined with gastric drainage

Vagotomy combined with other operations

It soon became evident that vagotomy alone was an unsatisfactory operation (Grimson Rundles Baylin, Taylor and Linberg, 1949, Pollock 1952, Rowe Grimson, Flowe Lyons Longino and Taylor, 1952, Walters and Chance, 1953) It was therefore, suggested that a drainage procedure should be added to the vagal section

Storer Woodward and Dragstedt (1950) found in Mann Williamson dogs that removal of the cephalic phase (vagectomy) protected half the number of animals while removal of the gastric phase (resection of the antrum) protected two-thirds of the number of animals That subtotal gastrectomy plus vagotomy does not necessarily completely abolish gastric secretion was reported by Cushing (1932), Klein Aschner and Krohn (1933) Shapiro and Berg (1934) Winkelstein and Berg (1938), Dragstedt and Owens (1943) Dragstedt Palmer, Schäfer and Hodges (1944), Portis (1944), Ruffin, Grimson and Smith (1946) Moore, Chapman Schulz and Jones (1947), Vanzant (1947), Oliver (1947 1951), Ruffin and White (1948)

According to Bockus (1948) there is no proof that gastro-enterostomy will invariably function satisfactorily in the vagotomized stomach But according to Crile (1951) the combined operation of vagotomy and gastro-enterostomy produces a synergistic effect and offers the most effective and safest surgical treatment for duodenal ulcer it produced a most satisfactory clinical result in 90 per cent of 147 patients after a follow up of 2 to 4 years (Hoerr, Brown, Rumsey and Crile 1951)

Walters and Chance (1953) now use gastro-enterostomy and gastro-enterostomy with vagotomy only in cases in which gastric resection seemed to carry an unreasonable risk when compared to that of gastro-enterostomy

Hoerr (1953) in 146 patients observed excellent results in 99 (68 per cent) and good results in 25 (17 per cent) Holt and Robinson (1954–55) claimed satisfactory results in 87 per cent of 243 cases of vagotomy and gastro-jejunostomy Weinstein, Druckerman, Lyons and Colp (1955) found a recurrence rate for gastro-enterostomy alone of 15 per cent, with vagotomy 10 per cent, subtotal gastrectomy 6 per cent with vagotomy 0 6 per cent

Imperato and Hinton (1955) observed the dumping syndrome in 2 3 per cent of 392 patients after subtotal gastrectomy, but in 26 per cent of 65 patients after subtotal gastrectomy plus vagotomy Bollman and Lloyd (1955) in 316 duodenal and marginal ulcers had excellent results in 84 3 per cent of 216 cases of gastro-enterostomy plus vagotomy, with recurrence

were free of recurrence after 3 years and of the gastro-enterostomies 10 of 14 patients had definite or suspected recurrence

Grimson, Baylin, Taylor, Hesser and Rundles (1947) observed that the secretory response of the stomach to histamine is considerably reduced after vagotomy White and Smithwick (1947) have pointed out that neurosurgical methods have failed to relieve hyperacidity because the essential mechanism which controls digestion lies in the intrinsic plexuses of the gastro-intestinal tract and that the preganglionic fibres of the vagus and sympathetic nerves have extraordinary powers of regeneration (Division of the vagi does not abolish the action of atropine, therefore, the intrinsic nervous system continues to function) Antia and Ivy (1949) studied dogs with fistulae before and after vagotomy The time required for 80 per cent emptying of a test meal of 250 millilitres of boiled milk or 200 millilitres of boiled milk plus 50 millilitres of corn oil was not significnatly altered for either meal by vagotomy, thus the inhibitory effect of fat was not changed by vagotomy

Orr and Johnson (1947) argued that patients with duodenal ulcer are typically subjects with hypermotile, hypersecreting stomachs, that the histamine beeswax method (Code and Varco, 1940) produces ulcers by continuous hypersecretion, that the side tracking of the alkaline secretions of the pancreas and the bile as shown by Mann and Williamson (1923) produces anastomotic ulcer that Stahnke (1924–25) claimed to produce ulcers by repeated stimulation of the vagi and ulcers associated with thalamic injury (Cushing, 1932) were probably due to vagal irritation They, therefore, justified vagotomy as a "physiological" solution of the peptic ulcer problem because vagal section eliminates the psychic phase of gastric secretion and reduces both the gastric motility and the quantity of free hydrochloric acid

The fallacy of this reasoning has been pointed out by the author (Spira, 1947, 1948) and it is now quite obvious that vagotomy cannot be considered as a "physiological" procedure

Derom (1948) has drawn attention to the grave atony following vagotomy which may affect not only the stomach but the duodenum as well He warns that post operative steps should be taken in order to anticipate this troublesome complication which may have a fatal issue

Alvarez (1948) found it interesting that "flurries of interest" in bi vagotomy had occurred in the years 1907–1914 1920–1924 and 1930–1934 and then died down, as so often happens The reasons for surgeons having given up the operation were not published

Govaerts and van Geertruyden (1949) after an extensive review of the subject, concluded that the indications for vagotomy are few (1) when the general condition of the patient with a gastro-enterostomy does not warrant a more extensive operation (2) for jejunal ulcer after extensive gastrectomy

Bockus (1950) referred to the "vagotomy epidemic of 1943 to 1948" because it was becoming increasingly evident that vagotomy alone for the cure of peptic ulcer, except gastrojejunal ulcer will not be employed in many clinics in the near future Walters, Belding and Lillie (1951) reached the

conclusion that there is little place for vagotomy alone in the treatment of duodenal ulcer and that it should not be performed for gastric ulceration because of the high incidence of unsuspected malignant disease and because the post-operative results compare unfavourably with gastric resection Pollock (1952) from a review of the collected results of vagotomy in 1,524 patients with peptic ulcer (1,314 duodenal 127 gastric, 82 jejunal and 1 oesophageal), concluded that vagotomy alone is an unsatisfactory operation but it yields better results when combined with gastric drainage

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in 5 per cent, and 95 4 per cent of 88 cases of a 50 per cent (limited) gastrectomy with no recurrence Coffey and Lazaro (1955) claim that a post operative follow up of 55 cases of vagotomy, hemigastrectomy and duodenostomy (Finney v Haberer) reveal certain conspicuous advantages of this operation

Beattie (1955) reported on 643 patients with chronic duodenal ulcer followed up for up to 8 years, treated with partial pylorectomy with resection of at least the anterior half of the pyloric sphincter and a subsequent pyloroplasty of the Judd type associated with vagotomy There was only one case of recurrent ulceration, 90 6 per cent were relieved permanently of all symptoms within 10 weeks and another 5 5 per cent restored to normal within 3 months Only 4 2 per cent were incomplete successes The overall mortality was 0 47 per cent (3 deaths, 2 from early imperfections of technique, 1 from post operative pneumonia)

Henson and Rob (1955), in 100 consecutive cases of duodenal ulcer treated by vagotomy and gastro enterostomy of which the first 45 showed an apparently satisfactory initial follow up, 9 (20 per cent) required further gastric surgery In this series (78 men and 22 women), of those which were followed up for 29 months excellent results were obtained in 33 patients (37 1 per cent), good results in 9 (10 1 per cent) Persistent post-operative syndromes occurred in 30 (33 7 per cent), persistent dyspepsia alone with unproved recurrence of ulceration in 5 (5 6 per cent) and proved recurrent ulceration in 11 (12 4 per cent) Because of the high recurrence rate in the course of a relatively short follow up period and the high incidence of post operative syndromes, they concluded that vagotomy and gastro-enterostomy is an unsatisfactory operation for duodenal ulcer

Sympathectomy

Vago-sympathectomy was suggested in order to oppose the over action of the vagus

Experimental observations

The experimental production of gastric lesions by section of the sympathetic nervous system has been considered in the Chapter on Experimental Ulcer

Peptic ulceration in dogs and rabbits following splanchnicectomy has been reported by Dalla Vedora (1902), Durante (1913), Brancati (1914), Koennecke (1922 1923, 1926), Alvarez, Hosoi Overgaard and Ascanio (1929) Koga (1937), and Lium (1941) Holmes (1953) found that with pyloric ligation, or in the Shay rat, simultaneous ganglionectomy alone was less effectual (50 per cent) than with added vagotomy which prevented ulceration in 90 per cent of the animals

It has already been suggested (*see* Physiological Considerations) that since the vagus and the gastric sympathetic are mixed nerves and do not behave strictly as antagonists, resection of the one reacts on the other and that the one may then assume to some extent the function of the other

Clinical observations

Many contradictory clinical observations have been published on this subject

Relief of pain and healing of the ulcer has been reported by Froehlich Stephan and Froehlich (1942) and Pereira (1944)

Sicard Albot and Tricard (1945) reported the results of splanchnicectomy for gastro-duodenal ulcer in 8 patients There was some relief of pain for a few months but no change in the ulcer crater 5 patients were submitted to gastric resection within 18 months

Froehlich (1946) reported 25 cases of sympathectomy in the treatment of peptic ulcer with excellent results in 9 cases good results in 5, 3 cases of ulcer persisted, but the patients attended to their work, 5 cases had bad results the results in 3 were unknown The author did not deny that the general results do not speak in favour of splanchnicectomy

Blegen and Kintner (1947) reported the aggravation of gastric ulcer in two patients after dorsolumbar sympathectomy, one patient had repeated haemorrhages during convalescence from the operation and the second had a painless perforation from which he died

Torre and Villareal (1948) observed in a case in which Smithwick s sympathectomy was performed a marked increase in peristalsis Siris (1948) claimed that sympathectomy relieved hypermotility, spasm of the duodenum and heartburn of 15 years standing in a patient with hypertension Craig Morlock and Hightower (1950) observed no significant effect on the motility of the human gastric antrum

According to Goethals Borin (1949) total denervation of the stomach was suggested by Schiassi (1911), Latarjet (1922) Latarjet and Wertheimer (1923), Gianolla (1925), Foucault (1938), and splanchnicectomy by Alba nese (1940), Froehlich (1942) Goethals Borin (1946), Pereira (1946) Otermin Andreu and Pueyo (1948) and Baumgarten (1948)

Goethals Borin (1949) stated that the following facts justify sympathectomy for peptic ulcers (1) the ulcer patient is an orthosympathicotonic, vagotonia is a secondary manifestation due to an increase of sympathetic tonus, (2) the psychic and central nervous system manifestations of ulcer which produce increased motor and secretory functions of the gastric mucosa are susceptible to modification by splanchnicectomy (3) the hyper histaminaemia which exists in the ulcer patient and produces a local ischaemia could be corrected by splanchnicectomy, (4) splanchnicectomy abolishes pyloric spasm increases gastric tonus and allows rapid evacuation of the acid gastric juices He suggested as a physiopathological hypothesis that splanchnicectomy abolishes the visceral reflexes originating in the stomach that it diminishes vagus irritability and therefore reduces psychic hyperchlorhydria and that the vasodilatation of the gastro-duodenal region accelerates the healing of the ulcer From his own observations he concluded that the problem is far from solved and that a combined vagotomy plus splanchnicectomy may be the answer

Mason and Pollard (1949) reported on the results of bilateral supra diaphragmatic splanchnicectomy and lower dorsal ganglionectomy as treatment for essential hypertension in a group of 1,498 patients over 11 years In 13 of these cases, with peptic ulcer, pre operatively 3 had proved, 4 had presumptive and 1 had a likely peptic ulcer, post operatively 9 cases had proved and 3 presumptive peptic ulcer They pointed out that ulcers advanced to dangerous proportions without giving the usual warning because pain pathways were not intact

Craig, Morlock and Hightower (1950) reviewed 963 cases in which sympathectomy was performed for the relief of severe essential hypertension, there were 22 cases of proved gastro-intestinal disease 20 with duodenal ulcer and 1 with gastrojejunal ulcer In 8 symptoms were unaltered, in 3 they became worse and in 3 less severe Symptoms of duodenal ulcer developed for the first time following sympathectomy in 7 (0 74 per cent) Ross and Brolsma (1951) in a review of 214 patients found that the incidence of peptic ulcer was not altered by this operation

Job and Villinger (1951) and Kux (1952) reported on 350 cases of sympathectomy with no fatalities The operation consists of a transpleural sympathectomy in the costo pleural sinus under local anaesthesia preceded by a pneumothorax which is aspirated after operation They claim good results in 63 per cent of 110 patients followed up for one and a half years But Kux now recommends a combined vagotomy and sympathectomy which gives better results

Boller (1953) reported the case of a man who had a history of dyspepsia from the age of 16 and when 22 years old had a retrocolic Billroth II operation for a high gastric ulcer which healed It was soon followed by a jejunal ulcer which was treated by high gastric resection, the patient was then transferred to Kux who performed transthoracic splanchnic and sympathetic section on both sides and right sided vagotomy, nevertheless, Banthine had to be administered to relieve pain A large ulcer appeared in the gastric remnant, a serious haematemesis occurred and the ulcer perforated into the transverse colon Total gastrectomy and partial resection of the small intestine and colon had to be performed

Conflicting surgical methods of treatment

Based on the assumption that hydrochloric acid is the element responsible for the causation of chronic gastro-duodenal ulcer, it is claimed that all surgical methods have a physiological principle as the basis of approach to the problem Thus, gastro-enterostomy was suggested as a mechanism which would bring about the neutralisation of hydrochloric acid by regurgitation of the alkaline intestinal secretions, gastrectomy was suggested in order to bring about the removal by amputation of the acid secreting area and vagotomy was introduced to prevent the development of hydrochloric acid by eliminating the mechanism of its production

However, results did not come up to expectations and the surgeons have now resorted to a combination of two methods, gastrectomy or gastro-

enterostomy with vagotomy, or a combination of vagotomy and sympathectomy

The results reported by the surgeons are most conflicting and appear to depend more on enthusiasm and personal idiosyncrasies than on the basis of their physiological claims. Optimistic reports encourage large scale trials but, unfortunately, as time goes on and wider experience is gained more failures are registered and disappointment gradually leads to the final abandonment of the innovations

Ogilvie (1956) states that the following can be labelled, after long trial, as unsuccessful experiments in the surgical treatment of peptic ulceration Gastro-jejunostomy, * gastro-jejunostomy with Roux loop, * gastro-jejunostomy with entero-anastomosis, gastro-duodenostomy pyloroplasty, Finney's operation local excision of gastric ulcer wedge resection of the stomach, sleeve resection of the stomach fundusectomy, proximal gastrectomy, * vasoligation, * vagotomy alone, vagotomy with gastro-jejunostomy Visick's ultra radical gastrectomy, * Devine's exclusion gastrectomy * physiological gastrectomy with pyloric conservation (Ogilvie, 1935) * gastrectomy with Roux-en-Y anastomosis * gastrectomy with entero-anastomosis gastrectomy with colonic replacement gastrectomy with jejunal replacement gastrectomy with duodeno-jejunal transposition. All these have been launched with a flourish of trumpets Only two have been apologised for All should be discouraged and those marked with an asterisk should be prohibited

The divergence of views between the orthodox and the author's conception of the problem arises from a different interpretation of the available data.

The orthodox conception of the disease is based on an inborn, constitutional element which is difficult to influence and, therefore, restricts the treatment which must remain symptomatic.

The author's conception is based on an acquired, environmental element which, therefore, makes it possible to influence the causative factor by changing the environment

CHAPTER 24

TREATMENT OF PERFORATION AND HAEMORRHAGE

For the pathological aspect of the problem reference should be made to the chapter dealing with the Pathological Considerations

PERFORATION

Treatment of perforation is a subject in which the physician takes little part except to arrange for the patient's admission to hospital at the earliest possible moment, once admitted appropriate pre operative treatment *should be instituted without delay*

There are three methods of dealing with this emergency (1) continuous suction, (2) immediate operative repair (simple suture), or (3) gastrectomy The choice of method must depend on circumstances at the time of admission *and the attitude of the surgeon*

Continuous suction

Wangensteen (1935) reported 4 late cases treated by continuous suction, *3 recovered, and 1 died (admitted 28 hours after the perforation) Bedford* Turner (1945) reported recovery in 6 patients, Taylor (1946, 1951) reported 24 recoveries in 28 consecutive patients (3 died of causes unconnected with the treatment and one might have been saved by immediate operation) *Olson and Norgore (1946) have abandoned this method and use it only in* patients who refuse emergency operations Stead (1951) reported 50 cases with 5 deaths, 4 of which were unfit for operation on admission Taylor and Warren (1956) making the fundamentally important distinction between *the acute and chronic ulcers, reported 47 patients with acute ulcer treated* by aspiration who recovered without complications and who showed no tendency towards subsequent chronic ulceration

Simple suture

Simple closure by suture, with or without omental graft, appears to be the operation of choice (Wangensteen 1935, Graham 1946, Barntell 1947) The object should be to cure the perforation and not the ulcer (Colp and Druckerman, 1946) Simple suture was advised by Bockus (1944) Mage and Payson (1952) Gilmour (1953), Schmitz, Harkins, Olson, Moore and Merendino (1953), Donhauser (1954) and Eagleson (1954) Parker (1941) in

a collected review for 1925 to 1938, of 764 cases treated by simple suture found that the percentage of cases who remained well varied from 14 per cent to 86 per cent On an average 388 or 51 per cent remained well and 376 or 49 per cent did not remain well In 524 cases followed up 96 (18 per cent) were subjected to a second operation Forty (1946) reported that, of 100 cases in which 70 were followed up, 10 required a second operation Illingworth Scott and Jamieson (1946) have drawn attention to the cumulative incidence of recurrence In 596 cases 65 8 per cent remained symptom free after one year of 166 cases followed up for 5 years 28 3 per cent remained symptom free and 20 per cent required further operation Ivy Grossman and Bachrach (1950) in a collected series of 1,106 cases followed up since 1940 found 33 per cent (range 5 6 to 67 9 per cent) were symptom free 66 7 per cent (range 32 1 to 94 4 per cent) had a recurrence of symptoms of 1,065 cases 18 per cent (range 13 5 to 33 3 per cent) required a second operation They considered that the literature on the severity of recurrences is too heterogeneous for statistical evaluation

It should be noted that in these statistics the basic distribution of acute and chronic ulcer has not been taken into account

Mortality rate

Graham (1946) reported 8 deaths (6 4 per cent) in 125 consecutive patients, Baritell (1947) 1 in 88 patients and Sangster (1948) 4 in 105 patients Jones Doll Jones and White (1953) 10 in 301 patients (3 3 per cent) Gilmour (1953) reported in 119 (58 per cent) cases of acute ulcer a mortality of nil and in 87 (42 per cent) of chronic ulcer a mortality of 15 per cent

Gastrectomy

Immediate gastrectomy for perforation was recommended by Haberer (1919) Strauss (1944), Nuboer (1951) Turner (1951), Auchincloss (1952) Carayannopoulos and Christopoulos (1952) Lowdon (1952) Emmett and Owen (1953) Moore Harkins and Merendino (1954) and Cooley Jordan Brockman and De Bakey (1955)

Mortality rates

Judin (1937) reported a 7 8 per cent mortality rate in 231 selected patients (representing 30 per cent of the total) Bobbio (1948) 8 deaths in 136 selected patients Heslop Bullogh and Brun (1952) 8 6 per cent in 104 patients Lowdon (1952) reported on 65 cases 51 primary partial gastrectomies with no mortality

The mortality rate is greatly influenced by the time interval between the perforation and the operation In 7,683 cases reported by De Bakey (1940) the mortality rate was 10 5 per cent after an interval of 6 hours 21 4 per cent after 12 hours 38 5 per cent after 18 hours 62 4 per cent after 24 hours

It is also affected by the time of the meal preceding the perforation rises

with the age of the patient (Ulfelder and Allen, 1942) and varies according to whether the ulcer is acute or chronic (Gilmour, 1953)

The longer the duration of the previous ulcer history before perforation the greater the likelihood of a recurrence of symptoms (Houston, 1946, Forty, 1946, Illingworth, Scott and Jamieson 1946)

Shock

Moynihan (1910), who has given a classical description of perforation which makes the diagnosis unmistakable, reported that shock was not present, an observation confirmed by Wangensteen (1935), Soutter (1941), and Barber and Madden (1943)

The success of all surgical interventions for perforation appears to depend on the technique of the surgeon, organized teamwork, choice of operation and selection of patient

HAEMORRHAGE

Treatment of haemorrhage must engage the combined attention of the physician and surgeon It cannot be too strongly emphasized that each case of haemorrhage must be considered as an individual problem

As soon as the gastric haemorrhage has been diagnosed, arrangements should be made for the immediate removal of the patient to hospital where he should be put to bed without undue delay, kept warm, reassured and given an injection of morphine to control restlessness

Blood transfusions

Whatever the cause of the bleeding it is essential to ascertain at the earliest possible moment the amount of blood lost and fluid requirements for the correction of dehydration (Bennett, Dow, Lander and Wright, 1938, Bennett, Dow and Wright, 1942) The necessary investigations must be undertaken by trained laboratory assistants The transfusion must be adequate and should be repeated as often as necessary If the right blood is not available, plasma may be given as a temporary substitute

Costello (1949), in a study of 300 cases of massive haematemesis, which included 171 cases of chronic duodenal ulcer, found that of the 75 patients who died 71 had not received adequate blood replacement Fatalities due to inadequate transfusions have been reported by Chinn and Weckesser (1951), Shapiro and Schiff (1952) Ogilvie, Cardoe and Bentley (1952), Saltzstein, Mahlin and Scheinberg (1953)

In addition to its life saving properties blood transfusion has the therapeutic advantages of stopping the bleeding combating infection and giving the patient a feeling of security and a sense of well being Special precautions, however must be taken in its administration and its highly specialized technique must be left to the expert

Diet

The patient s general strength must be maintained by a liberal diet and food should be given at usual meal times Starvation has now been generally

abandoned The modern tendency is to prescribe a full diet, Meulengracht s (1935) regime or one of its modifications, and the author goes even further and allows the patient to choose from his standard diet chart the items to his own liking Unless the haemorrhage is very severe the patient may feed himself Avery Jones (1943) found that prompt feeding and liberal transfusions have considerably decreased the incidence of recurrent bleeding

It may be of interest to mention a case reported by Graham (1941), of a patient who was admitted to hospital suffering from recurring massive haemorrhage from a duodenal ulcer The usual dietetic control with milk and cream, supplemented by eighteen transfusions of varying volume and at varying intervals failed to control the haemorrhage His haemoglobin, eight weeks after admission was 25 per cent. The patient was then placed on a full ward diet containing an abundance of animal protein with vegetables cooked and raw In Graham s words "The improvement in the patient was nothing short of phenomenal

Source of bleeding

The next step is to decide whether the source of bleeding is intragastric or extragastric

Rivers and Wilbur (1932) reported that 90·5 per cent were intragastric lesions Bockus (1944), after reviewing the literature, estimated that 60 to 75 per cent of all massive haemorrhages in the upper alimentary tract are caused by peptic ulcer Crohn Marshak and Galinski (1948) reported that out of 102 cases 59 were duodenal and 5 gastric ulcers 16 were due to miscellaneous causes and 22 were negative or unexplained In 363 cases reported by Welch (1949), 251 were accounted for by gastric and duodenal ulcer Moschkowitz, Mage and Kugel (1949) had 89 per cent of intra gastric lesions and Amendola (1949) 85 per cent. Tanner (1951) in 946 cases of haemorrhage found that 717 had gastric or duodenal ulcer 57 gastritis 29 carcinoma of the stomach and 34 portal hypertension

Treatment for intragastric bleeding

When it has been decided that the bleeding is intragastric then the next problem to be dealt with is the choice between medical and surgical treat ment a choice which should not be delayed for longer than 48 hours If, during this period the bleeding stops then the treatment which has been adopted can be continued under vigilant care If on the other hand the bleeding persists or recurs then the medical advisers are faced with the immediate question of whether the lesion is acute or chronic a diagnosis which may be difficult to arrive at within the stated period but which has a direct bearing on the choice of treatment.

In the acute ulcer haemorrhage occurs without any warning The patient does not complain of pain, he may feel giddy and faint his symptoms being due to loss of blood, often fainting in the bathroom

The chronic ulcer, on the other hand is associated with a long history

of pain During a period of quiescence, that is when the ulcer is healing and the morbid process is in abeyance, the ulcer does not bleed

The relative incidence of acute and chronic ulcer was reported by Nielsen (1922) as 16 acute and 32 chronic ulcers and an additional 11 ulcers plus scars, and 7 undetermined, Burger and Hartfall (1934) had 15 acute and 30 chronic ulcers

Avery Jones (1943) reported 51 cases (of which 38 were gastroscoped), as 21 acute ulcers, 2 acute gastritis, 15 undiagnosed Heuer (1946) reported 61 acute and 163 chronic ulcers, Schiff and Shapiro (1951) 10 per cent acute ulcers in 339 patients, Avery Jones (1952) in 1,053 patients, 329 acute and 724 chronic ulcers

The tendency to bleed is greater the later the ulcer begins (Stolte, 1944) According to Markoff (1954) the acute ulcer bleeds more than the chronic one

Haemorrhage as a first symptom, "silent ulcer" or acute ulcer, was reported by Burger and Hartfall (1934) in 6 8 per cent of 137 cases, by Kalk (1936) in 6 4 per cent of 154, by Andresen (1939) in 14 1 per cent of 120, by Woldman (1941) in 20 per cent of 144, by Rafsky and Weingarten (1942) in 15 2 per cent of 283, by Wilkinson and Tracey (1946) in 50 per cent of 140, and by Eads (1946) in 10 8 per cent of 129 cases Ivy, Grossman and Bachrach (1950), in 1,678 collected cases, found 16 2 per cent with no previous history If the diagnosis of acute ulcer has been established then surgery should be avoided Hinton and Church (1942) are emphatic that when there is no pain, there is no surgery

Avery-Jones (1943) reported 161 cases of proved or probable peptic ulcer with 14 deaths (9 per cent), 51 cases of acute ulcer with 1 death (admitted moribund)

Haemorrhage from an acute lesion seldom ends fatally Avery Jones (1952) reported 329 patients out of 1,020 as being in the acute lesion group, 8 of these died (all over the age of 65)

Brandon (*Lancet*, 1 360, 1956), reported encouraging results with adrenaline and Russell s viper venom given through a stomach tube

Comparative mortality rates of medical and surgical treatment

Early statistics on mortality rates are widely divergent and cannot serve as a basis for comparison because they do not refer to identical cases (Finsterer, 1939) Thus for medical treatment Chiesman (1932) recorded a mortality of 25 per cent in 191 patients, while Witts (1937) reported a death rate of 0 per cent in 24 cases, he did not think that the relative merits of operative and non-operative treatment of gastro duodenal haemorrhage could be assessed on mass hospital statistics, the best individual medical results (Meulengracht, 1936) being much superior to the best individual surgical results Meulengracht (1937) reported 1 36 per cent in 368 cases, and in 1947 on 1,031 cases with a gross mortality of 2 5 per cent and a net mortality (excluding causes other than bleeding) of 1 5 per cent

Meyer, Sorter and Necheles (1942) reported a mortality of 7 2 per cent

in medically treated and 22 2 per cent in surgically treated cases Andresen (1948) had only a 2 per cent mortality with medical treatment

Fraser and West (1949) in a series of 177 cases had a mortality rate of 6 2 per cent, 165 cases were treated medically, with a mortality of 4 2 per cent, the remaining 12 cases which did not show a satisfactory response to conservative treatment and were operated in the late period (that is after more than 48 hours of rapid blood loss) showed a mortality of 33 3 per cent Arteriosclerosis appeared to be one of the most important contributary causes of death

Chinn and Weckesser (1951) found that in 322 cases (1935–1948) treated medically, 211 did not bleed while in hospital, with 3 (1 4 per cent) deaths, 54 did bleed with 25 (46 per cent) deaths, 27 were operated on with 9 (33 per cent) deaths Of the 28 deaths occurring in those treated medically 19 had serious complicating diseases

Ogilvie, Cardoe and Bentley (1952) found in 358 cases (of which 106, or 30 per cent were over 60) that the bleeding was arrested in 339 cases and 35 (10 per cent) came to operation The overall mortality of 19 cases was 5 3 per cent, in 8 cases a fatal issue was inevitable, 4 were due to errors of judgment, in 4 transfusion was inadequate in 2 an excess of intravenous fluid was given, and in 1 an aberrant pancreatic duct was severed

Saltzstein, Mahlin and Scheinberg (1953) reported mortality in 271 medical cases as 5 1 per cent, and in 68 surgical cases as 5 9 per cent

Mortality rates for surgical interventions vary Finsterer (1939) claims 4 2 per cent, Gordon Taylor (1945) 10 to 11 per cent, Parsons and Aldridge (1950) 14 per cent

Increase in the fatality rate with age was shown by Blackford and Allen (1942) in a series of 120 men and 31 women There was 1 death in the 20 year age group 1 in the 30 year and 6 in the 40 to 45 year group Similar observations were made by Allen (1937), Blackford and Williams (1940) Meyer Sorter and Necheles (1942) reported with conservative treatment, no fatalities under 45 years, 21 per cent in patients over that age, Rafsky and Weingarten (1942) 4 8 per cent in those under 50 16 8 per cent in those over 50, Cates (1950) 92 per cent in those over 45

Over fifties are poor risks whether treated medically or surgically (Lewin and Truelove, 1949)

Indications for surgical treatment

Indications for surgery are (a) definite proof of chronic ulcer and (b) the age of the patient (over 50)

Hurst and Ryle (1937) reserved operation for the rare cases in which the source of bleeding is a large hole in a sclerotic vessel exposed at the base of a chronic ulcer MacKay (1954) pointed out that the pathological changes in the vessels in peptic ulcer are secondary to the inflammatory process in the ulcer area these changes render the vessels less elastic impair their contrac tility and prevent smooth coaption of their intima They occur regardless of

age and are not related to generalized arteriosclerosis According to Osborn (1954) gastric arteries of all ages are immune to arteriosclerosis

Recurrence of haemorrhage after conservative treatment was reported by Haraldson (1948) in 205 out of 504 patients after 10 years (3 fatal) Holman (1948) found that 26 to 50 per cent bled again, with a death rate of 3 7 per cent

Haemorrhage as a secondary manifestation

Since haemorrhage is considered by the author (as explained in the Pathological Considerations) as a secondary manifestation of a septic focus located outside the gastro-duodenal region an attempt should be made to discover the primary disease It will be found that the gall bladder and colon are frequently implicated and this can be confirmed by further investigations When the correct diagnosis has been established, appropriate treatment can then be instituted and the future of the patient greatly safeguarded

Tanner (1951) reported the significant observation that 50 per cent of his cases of gastritis and uncertain pathology were associated with achlorhydria Swynnerton and Tanner (1954) reported that of 403 patients with achlorhydria one in three had manifest haemorrhage at one stage during the course of the disease

The following two case reports illustrate the author's approach to the problem

Case No 1 — H P aged 49 when first seen on 12 7 44 gave a history of stomach troubles for 30 years For 4 to 5 years he had an indefinite pain under the ribs which made him feel very ill this was associated with vomiting at night only An x ray report in 1943 showed a duodenal scar Seven weeks prior to his visit he had an attack of haematemesis and was put on the Sippy diet given iron and vitamin C. On examination the abdomen was generally tender with no definite epigastric tenderness There was also some superficial hypertrophic glossitis the appetite was fair the bowels regular but the stools rather offensive (for which he had had treatment three years previously) X ray examination five days later showed a very deformed duodenal cap and a small ulcer The patient was given bismuth subnitrate 10 grammes before breakfast (Bensaude s method) and dilute hydrochloric acid three times a day His improvement was rapid. X ray on 27 7 44 (ten days later) showed a deformed cap which was not tender on pressure His health remained good till September 1951 when he reported that he had a peculiar feeling in the head and had passed a dark brown stool He was given a bowel antiseptic and had no further trouble until he had a small haemorrhage in August 1954 *which was associated with offensive stools The treatment was repeated* with the addition of large doses of the vitamin B complex. In the summer of 1955 he had a successful removal of an acoustic neuroma he has had no further recurrence of bleeding

Case No 2 — J H W aged 51 when first seen on August 30th 1953 gave the following history

January 1939 appendix removed 1940 abdominal discomfort diagnosed by his doctor as duodenal ulcer x ray, 1941 — no ulcer but duodenitis x ray 1942 R A F Hospital — no ulcer x ray, 1944 Nova Scotia — no ulcer, summer 1945 cholecystogram — negative January 1946 cholecystectomy for cholecystitis and gall-stones (normal stomach and duodenum) January, 1947 melaena, x ray two months later — no ulcer In August, 1950 complained of considerable pain, which was not diagnosed

he insisted on laparotomy which disclosed extensive adhesions between duodenum and gall bladder fossa and a chronic ulcer in second part of the duodenum penetrating head of the pancreas an antecolic Polya partial gastrectomy was performed. Occasional dyspepsia in 1952 On August 28th, 1953, melaena August 30th recurrence of melaena admitted to hospital Barium meal September 15th, 1953 — no ulcer

After his discharge from hospital the patient complained of very offensive stools and therefore an intestinal antiseptic was prescribed The patient kept well but early in 1954 required a further course of the intestinal antiseptic because his stools were un pleasant On 1 1 1956 the patient reported that during the whole of 1954 and 1955 he "enjoyed *perfect* health as never before

THE "ULCER MENTALITY"

It need not be emphasised that the relation of the doctor to the patient involves, in addition to his professional duties, many moral obligations He must inspire the patient with the utmost confidence, which he can only achieve by a complete mastery of his subject He must be prepared to face difficult situations and answer awkward questions with circumspection and tact He must be frank and outspoken but be conscious of his responsibilities and admit ignorance when the occasion arises

The question which is uppermost in the patient's mind is whether he is suffering from cancer As a general rule, the patient should never be told that there may be even a suspicion of malignant disease Only under very exceptional circumstances should this rule be broken

If the physician is satisfied that he is dealing with a benign lesion, he must immediately reassure the patient and make it clear to him that, generally speaking, chronic ulcers do not perforate, bleed, or become malignant He should explain that the ulcer exists only during the periods of activity when pain is present, and that, when there is no pain, the quiescent period corresponds to the stage of healing Providing the patient adheres to a rational mode of living during this period he can ignore the existence of an ulcer

To advise, as suggested by Crohn (1944), that cures are effective but generally temporary and that to obtain a lasting cure the patient must relax, observe his diet, eat every two hours until bedtime, try to ward off anxieties indulge in light recreation, take a vacation and seek a change of scene as often as possible, cease smoking avoid intoxicants and take precautions against colds, is to imply that the patient must be a millionaire and attend to himself all day in order to keep in a tolerable state of health!

To consider peptic ulcer as an incurable disease (Althausen, 1949) and tell the patient to adjust his life to the ulcer is a defeatist attitude which must be repudiated Likewise the suggestion that "once an ulcer patient, always an ulcer patient" (Ivy Grossman and Bachrach, *1950) must be strongly* condemned as it creates the "ulcer mentality" and passes an undeserved life sentence of mental anguish on an innocent human being

CHAPTER 25

THE AUTHOR'S STANDARD TREATMENT

Based on the physiological and pathological principles, as previously shown, a method of treatment has been evolved which has completely justified itself in practice

It consists essentially in (1) a dietary regime which has a low fat content, the details of which are given in the Diet Chart, and (2) the administration of small doses of alkali for the control of the excess of acid which is always present with chronic ulcer

As a rule the treatment is ambulatory and there is no need to put the patient to bed Short periods of rest after meals, and the application of dry heat (a hot water bottle or an electric pad) to the epigastrium are all that is required Meals should be taken in the usual way, that is, at normal meal times

A mixture of soluble and insoluble alkalis containing say, 10 grains each of bicarbonate of soda, magnesium carbonate and calcium carbonate in half a tumblerful of water should be given a few minutes before meals, 5 minims of tincture of belladonna may be added if the pain does not respond to the alkali mixture The alkaline treatment may be reduced after 1 to 2 weeks and can generally be omitted after 6 weeks

Patients who have been on a restricted diet for a long time and who show vitamin deficiencies should be given the appropriate vitamins in generous doses

Nervous patients may require small doses of sedatives which should always be administered in a soluble form because it is less toxic, and rapidly excreted Sodium phenobarbitone ½ grain twice or three times a day for a short period may contribute to the patient s feeling of well being

Constipation, which is the usual concommitant of ulcer will require little additional medication whilst the patient is taking the alkaline mixture If the bowel needs additional help it should be provided in the form of bland preparations which produce bulk rather than colonic stimulation *

It has been emphasised (Spira 1931) that if this treatment does not produce rapid improvement in the condition of the patient, it is not the treatment but the diagnosis which is at fault and further investigation should be instituted without delay

A few cases illustrative of the author s results are given in plates I–XVI Only radiographs of gastric ulcers have been presented because they are less liable to erroneous interpretation than radiographs of duodenal ulcers

* Constipation is the curse of modern civili ation which may be medically defined as the struggle of getting food and the struggle of getting rid of it.

'Animals feed, man eats the man of intellect alone knows how to eat
Brillat Savarin

The proof of the pudding is in the eating
Old Proverb

THE DIET CHART

The following diet chart has been constructed in the form of a menu in order to facilitate the choice of foods

Hors d oeuvres

All hors-d oeuvres are strictly forbidden, including caviare, smoked salmon and smoked eel

Soups

ALLOWED

Clear chicken broth consommé bouillon and julienne all fat having been carefully removed these may be followed later by thick soups (not thickened with milk or cream) such as cream of rice, cream of wheat, cream of peas all without fat and in small quantities

Method of preparation

Meat essences must *not* be used It is advisable to prepare soups the day before they are required for consumption so that when cold all fat can be easily removed.

Fish and shell fish

ALLOWED

Sole plaice turbot halibut whiting fresh haddock cod hake smelt all fresh water fish

Lobster and crab, prawns and shrimps oysters

NOT ALLOWED

Salmon, mackerel herring eel, bloater whitebait smoked fish preserved fish, sardines and anchovies, mussels fish pastes

Method of preparation

Fish should be rather overdone than underdone it can be eaten hot or cold It may be boiled steamed grilled or fried (the batter must not be consumed) Fried fish can be eaten hot when fried in butter or preferably in margarine or cold when fried in oil Salt and lemon may be added to taste

Method of frying in oil — Dry the fish well in a cloth sprinkle with flour shake off any superfluous flour dip into a beaten egg and immerse when the oil is sufficiently hot to show a blue smoke When the fish is golden brown remove and drain thoroughly

Meat

ALLOWED

All meats beef mutton veal lamb pork (without crackling) fried bacon without fat calf s liver kidney sheep s brain calf s foot jelly smoked meats ham tongue

NOT ALLOWED

Stews Irish stew goulash oxtail boiled meat and twice cooked meat braised meat meat puddings, pies and patties minced meat, curry tripe sausages of all kinds *Paté de foie gras* meat pastes relishes

Method of preparation

All visible fat must be rigorously removed Dripping should not be used. It is important that all meat should be tender It does not require mincing It may be eaten hot or cold. Meat should be grilled or roasted. Red meat should be underdone white meat rather well-done Salt and pepper may be added to taste

Pure meat gravy from the joint *without fat* is permitted. Prepared sauces gravies mustard pickles condiments and spices chutney are *not allowed* and nothing should be added to make the dish rich

Fat used for cooking should not be used more than twice

Poultry

ALLOWED

In the initial stages all young birds are allowed In the later stages small quantities of breast of goose or duck *may be tried* The same applies to pheasant, partridge grouse.

NOT ALLOWED

Game and venison which require rich sauces
Stuffing bread sauce and fried breadcrumbs.
All poultry should be roasted not boiled or casseroled and eaten hot or cold.

Vegetables

ALLOWED

Potatoes and sweet potatoes all root vegetables carrots parsnips, beetroot turnips swedes vegetable marrow seakale and chicory young peas, French beans scarlet runners broad beans butter beans lentils and Indian corn without husk spinach tomatoes asparagus white and green artichokes, mustard and cress parsley

NOT ALLOWED

Onions, leeks and radishes celery and horse raddish cucumber water cress mushrooms

Cabbage cauliflower brussels sprouts spring greens cape brocoli and sauerkraut should be avoided in the initial stages of the treatment

Method of preparation

Potatoes should either be boiled or baked in their jackets not fried or sauté

Vegetables should be boiled in large quantities of water or better still boiled in two waters or submitted to pressure cooking Root vegetables are most digestible when they are prepared in the form of a purée In the later stages of treatment a little fresh butter may perhaps be added

In the after treatment the vegetables mentioned under Not allowed may be tried

Warmed up vegetables are *not allowed*

Salads

Green salads should be taken sparingly at first They are allowed when they are in season and only the tender lettuce leaves should be chosen.

Salad dressing

The dressing should consist of a minimum quantity of preferably arachis oil (huile d arachides) or the finest tasteless olive oil and a little tarragon or malt vinegar (in the proportion of 2 to 1) or lemon juice with salt to taste A little pepper and a pinch of sugar may be added.

Puddings and pastries

ALLOWED

Custards junket blanc manges and jellies plain cake

Milk puddings should be partaken of sparingly and only at meals where meat has not been consumed It is important that they should be baked slowly for about three to four hours, until their consistency is that of light cake

NOT ALLOWED

Pancakes apple-fritters which absorb the grease in which they are cooked.

Suet puddings fancy pastries

Fruit

ALLOWED

All fruits may be eaten fresh but must be ripe Preserved dried and stewed fruits are allowed provided they are not too acid. When acid fruit is used for stewing a small quantity of bicarbonate of soda should be added before cooking to overcome the acidity Idiosyncrasies to fruits vary with individuals and their reactions must be carefully noted especially as regards berries

Bananas must be very ripe.

NOT ALLOWED

Melon and pineapple nuts chestnuts almonds and raisins Avocado pears.

Cereals and farinaceous foods

ALLOWED

Cereals such as Quaker Oats Grape Nuts, Force etc.

Rice tapioca semolina macaroni spaghetti and similar Italian pastes may be freely consumed.

Either salt or sugar can be added to taste Milk may also be added.

Bread and biscuits

ALLOWED

Bread and rolls must be stale and when toasted eaten cold White wholemeal, Hovis and Graham bread etc. Rye Vita Vita Wheat, water biscuits rusks and zwieback.

NOT ALLOWED

Hot buttered toast shortbread and other rich biscuits

Sweets

ALLOWED

Barley sugar fruit drops sugar in any form honey seedless jam and marmalade jelly can be partaken of freely

NOT ALLOWED

Chocolate toffee butterscotch

Cheese and butter

ALLOWED

Pommel Gervais and fresh cream cheese — Port Salut, young Dutch and mild cheese in general may be tried.

NOT ALLOWED

Ripe and blue cheese are strictly forbidden.

Butter or margarine should only be eaten fresh and in small quantities. On no account should butter and cheese which have been submitted to heat be consumed or used as an adjunct to sauces or gravies

Eggs

Eggs in every form are *strictly forbidden except in the preparation of custard and cake*

Milk and cream

ALLOWED

Sour milk yoghourt koumiss whey and buttermilk — Horlicks (prepared with water)

NOT ALLOWED

Citrated peptonized condensed and dried milk.

Cow's milk *is forbidden except in small quantities in tea and coffee* It should be remembered that milk is not a natural food for adults and still much less a beverage than a food

Cream in all forms is *strictly forbidden* — cream ices are *not allowed* but water ices are permitted

Beverages

ALLOWED

Water is the beverage *par excellence* It can be flavoured to the patient's liking

All mineral waters Vichy Evian Vittel Malvern sodawater barley water, albumin water orange juice lemon juice tomato juice and fruit drinks

Weak tea infusions, tisanes and weak coffee may be tried

NOT ALLOWED

Hot milky drinks cocoa and chocolates

Ginger beer and ginger ale

Alcohol cocktails liqueurs and champagne are *strictly prohibited*

In the later stages wine with water may be tried When symptoms have disappeared mild beers can also be tried

INSTRUCTIONS TO THE PATIENT

As a general rule any dish which the patient dislikes or which gives rise to eructations or has been found by experience to be indigestible should be discontinued either the substance of the dish is contra indicated or the method of preparation faulty

Violent exercise particularly stooping bending lifting and gardening should be strictly avoided during treatment

Smoking in moderation after meals is allowed (Overindulgence may produce nicotine poisoning which gives bizarre symptoms intolerance to tobacco increases as one gets older)

APPENDIX

Cardiac Sphincter

Anatomy Keith (1903) Cannon (1911) Forssell (1912 1913) Leber (quoted by Forssell 1912) Alvarez (1922) Caballero (1923) Reich (1926), Hurst (1927) McSwiney (1928 29) Abel (1929) Knight (1934) Lendrum (1937) Maximov and Bloom (1948)

Physiology Langley (1899) Mikulicz (1903) Cannon (1908 09 1911) Cannon and Washburn (1912) Carlson and Luckhardt (1914) Carlson (1916) Thieding (1921) Carlson Boyd and Pearcy (1922) Jackson (1922) Mosher (1922) Brown and McSwiney (1926) Schilf (1926) Veach (1926) McSwiney (1928-29) Muller and Rieder (1931) Fulde (1933 34) Feldman and Morrison (1934 35) Lendrum (1937) Nemours Auguste (1951) Monges Monges and Gambarelli (1955)

Normal Peristalsis in the Oesophagus Meltzer (1899 1907) Meltzer and Auer (1907) Templeton and Moore (1944)

Reverse Peristalsis of the Oesophagus Cannon (1911) Carlson (1926) Holmes and Dresser (1928) Beams (1932) Barclay (1936) Alvarez (1945) Pennington, Haney and Youmans (1946)

The Nervous Control Rossbach (1890) Openchowski (1899) Courtade and Guyon (1899) Langley (1899) May (1904) Elliott (1904) Meltzer and Auer (1906 1907) Klee (1921) Thieding (1921) Rogers and Bercovitz (1921) Carlson and Luckhardt (1921) Koennecke (1922) Carlson Boyde and Pearcy (1922) Hatcher and Weiss (1923) McCrea McSwiney and Stopford (1925) Knight (1934) Mitchell (1938 39) Hwang Essex and Mann (1947)

Cardiospasm Zenker and Ziemssen (1878) Morrell Mackenzie (1884) Mikulicz (1904) Cannon (1906 07) Heyrowsky (1912 13) Hurst (1914-15) Shaw and Woo (1916 17) Shattock (1916-17) Hill (1918 19) Kelly (1920) Plummer and Vinson (1921) Rake (1926 1927) Morley (1927) Hurst (1927) Cameron (1927) Mosher and McGregor (1928) Soper and Cassidy (1929) Hurst and Rake (1930) Muller and Rieder (1931) Wood (1932) Sturtevant (1933) Knight (1934) Knight and Adamson (1935) Ferguson (1936) Lendrum (1937) Zeller and Burget (1937 1938) Brucke and Stern (1938) Grondahl and Haney (1940) Vinson (1940) Cowgill (1941) Lehmann and Koepfel (1942) Templeton and Moore (1944) Grimson Reeves Trent and Wilson (1946) Kuntz (1946) Hwang Essex and Mann (1947) McMahon Braceland and Moersch (1951) Jefferson Philips Proffitt and Necheles (1951) Necheles and Jefferson (1952)

The Sphincter of the common bile duct

Anatomy Vesalius (1543) Fallopius (1561) Glisson (1654) Haller (1666) Bianchus (1711) Vater (1720) Santorini (1724) Gage (1879) (all quoted by Boyden 1936) Tobien (1853) Gage (1878-79) Oddi (1887 1888) Hendrickson (1898) Letulle and Nattan Larrier (1898) Helly (1898) Rost (1913) Mann (1917 18 1920) Auster and Crohn (1922) Mann and Giordano (1923) Matsuno (1923) Mann (1924) Job (1926) Whitaker (1926) Higgins (1927) Giordano and Mann (1927) Burget and Brocklehurst (1927 28) Nuboer (1929) Lueth (1931 32) Dubois and Hunt (1932) Halpert (1932) Ivy (1934) Dardinski (1934-35) Schwegler and Boyden (1937) Boyden (1937) Gordon Taylor (1942) Long (1942)

Comparative Anatomy Higgins and Mann (1926) Burget and Brocklehurst (1927 28) Schmidt and Ivy (1937)

The Collus cysticus Sphincter Löhner (1924 1926) Winkelstein and Aschner (1925) Copher and Kodama (1926) Whitaker (1926) Boyden (1926 1928) Westphal and Gleichmann (1930) Bergh (1942)

Physiology

A The Nervous Control Oddi (1888) Doyon (1894) Meltzer (1917) Westphal (1923) Winkelstein (1923) Mann (1924) Carlson (1925) Burget (1925 1926) Whitaker (1926 1927) Boyden (1926) Kodama (1926) Copher and Kodama (1926) Potter and Mann

(1926) McMaster and Elman (1926) Boyden and Birch (1930) Birch and Boyden (1930) Lueth (1931) Puestow (1931) Ivy (1934) Boyden (1937) Walters McGowan and Butsch (1937) Puestow (1938) Boyden and Johnson (1941) Necheles and Kozoll (1942) Schulze and Boyden (1943), Boyden and Buskirk (1943) Johnson and Boyden (1943) Boyden Bergh and Layne (1943)

B The Chemical Control Oddi (1887) Doyon (1893, 1894), Archibald (1919) Reach (1920) Burget (1925), Cole (1925), Elman and McMaster (1926) Chiray and Pavel (1926) Brugsch and Horsters (1926) Whitaker (1927) Boyden (1927 1928) Boyden and Birch (1930) Crain and Walsh (1931) Puestow (1931) Sandblom Voegtlin and Ivy (1935) Doubilet and Colp (1937) Bergh (1942)

Normal Function of the Sphincter Archibald (1919), Lohner (1924 1926) Higgins and Mann (1926) Emerson and Whitaker (1928) Koster, Shapiro and Lerner (1936), Snape (1947) Smith, Walters and Beal (1952)

The effects of the Failure of the Sphincter Mechanism Opie (1901, 1910) Archibald and Mullaly (1913), Whipple and Cook (1918) Brock and Morel (1919) Archibald (1918 1919) (quoting Claude Bernard 1856 Hlava 1890, Polya 1906, Flexner 1900 1906 Opie 1910), Mann and Giordano (1923) Ivy (1930) Wangensteen Leven and Manson (1931) Bottin (1932) Jones (1932), Wolfer (1931, 1939), Bisgard and Baker (1940), Elman (1942)

The Ileo-Colic Sphincter

Anatomy Vidirus (1557) (quoted by Kellogg 1915) Variolus (1573) Bauhin (1579) Morgagni (1719) Winslow (1732), Albinus (1754) (all quoted by Testut 1922) Struthers (1893) Toldt (1894) Merkel (1899), Poirier and Charpy (1901), Keith (1903) Elliott (1904) Testut (1905) Symington (1906) Birmingham (1909) Cunningham (1912) Sobotta and McMurrich (1914) Rutherford (1914) Balli (1919) Hromada (1921) Beattie (1924) Plesch (1928) Walcker (1932) Hunter (1934) Oppenheimer (1940) Bargen Wesson and Jackman (1940) Rouviere (1943) Buirge (1944)

Physiology

Nervous Control Elliott (1904) Dale (1906) Short (1919) Hromada (1921), Toennis (1924 1928) Plesch (1928) Hinrichsen and Ivy (1931) Walcker (1932) Smets (1936)

Normal Function Bauhin (1579) Senn (1889) Generisch (1893), Dauriac (1893) Struthers (1893) Toldt (1894) Poirier and Charpy (1901) Katz and Winkler (1902) Barclay Smith (1902) Keith (1903) Elliott and Barclay Smith (1904) MacEwen (1904) Symington (1906) Birmingham (1909) Hurst (1909) Pavlov (1910) Cannon (1911) Singer and Holzknecht (1911) Cunningham (1912) Keith (1912) Kellogg (1913) Hertz (1913) Brosch (1914) Rutherford (1914) Dietlen (1914) Hannes (1920) Hromada (1921) Carman and Miller (1921) Heile (1921) Rost (1923) Toennis (1924) Alvarez (1924) Hurst (1925) Toennis Eichler (1927), Henderson (1928) Plesch (1928) Balli (1929) Hinrichsen and Ivy (1931) Walcker (1932) Winkler (1932) White Rainey Monaghan and Harris (1934) Stimson (1934) Rainey (1934) Chiray and Bosquet (1935) Sperling (1936) Larson and Bargen (1936) Puestow (1938) Barclay (1939) Alvarez (1940) Oppenheimer (1940) Buirge (1944) Golden (1945) Bustos (1950)

The Syndrome of Reverse Peristalsis

Barclay Smith (1902) Stierlin (1910) Boehm (1911) Bloch (1911) Cannon (1911) Rieder (1912) Norman and Eggston (1912) Case (1914) Cole (1914) Mutch (1914-15) Brown (1916) Whipple (1916) Draper (1922) Jones (1923) Boles (1924) Desmarest and Mercier (1924) Duroux (1927) Cunningham (1925) Hurst (1925) Hines Lueth and Ivy (1929) Rehfuss (1929) Berg (1930) Alvarez and Mayo (1931) Christensen (1931) Glassner (1932) Buckstein (1932) Stimson (1934) Almy and Tulin (1947) Alvarez (1948)

The Sphincter of the Vermiform Appendix

Anatomy and Physiology Treves (1902) MacEwen (1904) Christeller and Mayer (1929) Walcker (1932) Sperk (1933) Rieder (1936) Oppenheimer (1940) Wangensteen (1944)

PLATES

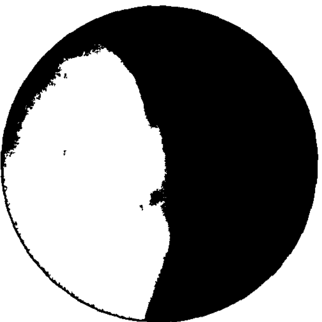


Figure 1

Figure 2

Figures 1–4 Mr W C F traveller aged 41 years first seen November 1943 History of indigestion since school days Complained of typical ulcer pain which woke him every night at 12 30 a m Radiological examination 14 12 43 showed a *posterior* wall *ulcer* (Fig 1) and *same on compression* (Fig 2) Standard treatment instituted pain disappeared after 3 days Further examination 18 1 44 showed ulcer crater completely healed (Fig 3) and *same on compression* (Fig 4)

Figure 3

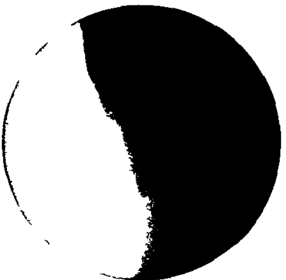


Figure 4

Figure 5

Figure 6



Figure 7

Figures 5 – 7 Mr F L handyman aged 65 years first seen January 1945 with a history of gastric pain of 8 years duration In 1936 was admitted to hospital with massive haematemesis which required several blood transfusions he remained in hospital for 5 months Radiological examination 4 1 45 showed large gastric ulcer (Fig 5) Standard treatment instituted Pain much relieved after one week Further examination 31 1 45 ulcer much reduced (Fig 6) Examined again 28 2 45 only trace of ulcer (Fig 7) This patient died one year later in hospital from cardiac failure due to auricular fibrillation and mitral disease



Figure 8



Figure 9

Figures 8–9 Mr H G C accountant aged 59 years first seen April 1944 with a long history of stomach trouble which was very severe for the last two years gastric pain woke him several times during the night He was examined radiologically six weeks prior to his visit the radiograph disclosing a large gastric ulcer of the lesser curvature (Fig 8) Standard treatment was instituted Pain ceased after a few days Radiological examination 16 5 44 ulcer much reduced (Fig 9)



Figure 10



Figure 11

Figures 10–11 Same patient (H G C) examined again *on* 9 6 44 small ulcer still visible (Fig 10) further examination 6 7 44 *no* ulcer (Fig 11) The patient reported again one year later when he complained of incoordination of gait but had had no gastric symptoms during the intervening period He was diagnosed as suffering from chronic barbiturate poisoning and admitted to hospital where he deteriorated rapidly with mental symptoms and died a week later At necropsy a large longitudinal scar was found on the lesser curvature which had broken down *post mortem* on one extremity



Figure 8



Figure 9

Figures 8–9 Mr H G C accountant aged 59 years first seen April 1944 with a long history of stomach trouble which was very severe for the last two years gastric pain woke him several times during the night He was examined radiologically six weeks prior to his visit the radiograph disclosing a large gastric ulcer of the lesser curvature (Fig 8) Standard treatment was instituted Pain ceased after a few days Radiological examination 16 5 44 ulcer much reduced (Fig 9)



Figure 14



Figure 15

Figures 14–15 Examined again 19 4 55 small ulcer still present (Fig 14) further examination 18 10 55 *no ulcer* (Fig 15) Reported 28 8 56 *having* had no symptoms and no treatment durin *the interval* radiological examination showed slight *irregularity* at seat of healed ulcer



Figure 1?



Figure 13

Figures 12–13 Mr H J S chauffeur aged 6) years first seen January 195) with a history of digestive trouble of three years duration Radiological examination 18 1 55 showed a large penetrating ulcer of posterior wall lesser curvature (Fig 12) Standard treatment was instituted but after one week he developed an acute infection complicated by pneumonia which kept him confined to bed for 3 weeks Radiological examination 22 3 5) mall lesser curve ulcer present (Fig 13)



Figure 18



Figure 19

Figures 16–19 Mr F J D administrator aged 56 years first seen September 1955 Had duodenal ulcer in 1946 confirmed by radiograph History of 2 months discomfort radiological examination at local hospital showed large gastric ulcer This was confirmed on 4 10 55 (Fig 16) Standard treatment was instituted rapid improvement Radiological examination 15 11 55 showed minute ulcer (Fig 17) and same on compression (Fig 18) Further examination 26 1 56 no ulcer (Fig 19) The patient has since remained in perfect health


Figure 16

Figure 17



Figure 22

Figure 23

Figures 22 – 23 Mr H W company director aged 47 years when first seen in October 1936 His medical history was as follows Joined the Army on the outbreak of World War I was invalided out one year later for gastritis Appendix removed in 1927 when a duodenal scar was seen at operation He complained of mild gastric symptoms which responded to symptomatic treatment He was seen one year later (1937) complaining of typical ulcer symptoms on his return from a 3 months continental tour when he did not keep to his diet Radiological examination 11 10 37 showed a deep posterior wall ulcer (Fig 22) Standard diet was resumed Further examination 21 10 37, ulcer present but smaller (Fig 23) Examined again 13 12 37 no ulcer crater (original films not available) He was seen in December 1938 and in July, 1940 when he complained of looseness of the bowel each time responding well to intestinal antiseptics He joined the Army and remained on active service training recruits for the duration of hostilities



Figure 20



Figure 21

Figures 20–21 Mrs S housewife aged 46 years first seen January 1953 with a history of 13 years indigestion and vomiting Diagnosed in 1945 and 1951 as chronic duodenal ulcer with pyloric obstruction Radiological examination 5 1 53 showed marked ptosis of the stomach with active peristalsis an ulcer crater was present in distal part of a long hypertrophied pylorus associated with a mass of inflammatory origin (Fig 20) The patient was advised to proceed with the surgical intervention which had been recommended by her home doctors As she had to wait some months for admission to hospital standard treatment was instituted Improvement was rapid Radiological examination 9 6 53 showed an irregular pyloric canal but no mass and disappearance of the ulcer (Fig 21) Three years after her first visit (6 1 56) she reported that although she led a very busy life she felt extremely well and had no symptoms



Figure 26



Figure 27

Figures 26–27 Further examination 16 12 52 (3 weeks later) ulcer crater still present but much smaller with some oedema and possibly infiltration (Fig 26) same on compression (Fig 27) As neoplastic changes could then not be excluded the patient was submitted to an exploratory operation an ulcer of the greater curvature was found which had penetrated and was adherent to the liver Partial gastrectomy was performed and the adherent part of the liver excised The pathological report confirmed the benign nature of the lesion Recovery was uneventful The patient reported 2 months later that he had never felt better in his life There has been no further trouble to date



Figure 24



Figure 25

Figures 24–25 Nothing was heard of Mr H W till November 1952 when he reported feeling very ill He had lost more than 3 stone since the beginning of the War He had no appetite complained of loose stools and was taking large quantities of alkaline mixtures his sleep was undisturbed Examination disclosed marked chronic superficial glossitis tenderness on deep pressure over the sigmoid but none over the epigastrium Large doses of vitamin B_2 and B_{12} were prescribed and all other medication stopped Symptoms improved almost immediately Radiological examination 25 11 52 showed a large ulcer crater on greater curvature with no evidence of neoplasm (Fig 24) same on compression (Fig 25)

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